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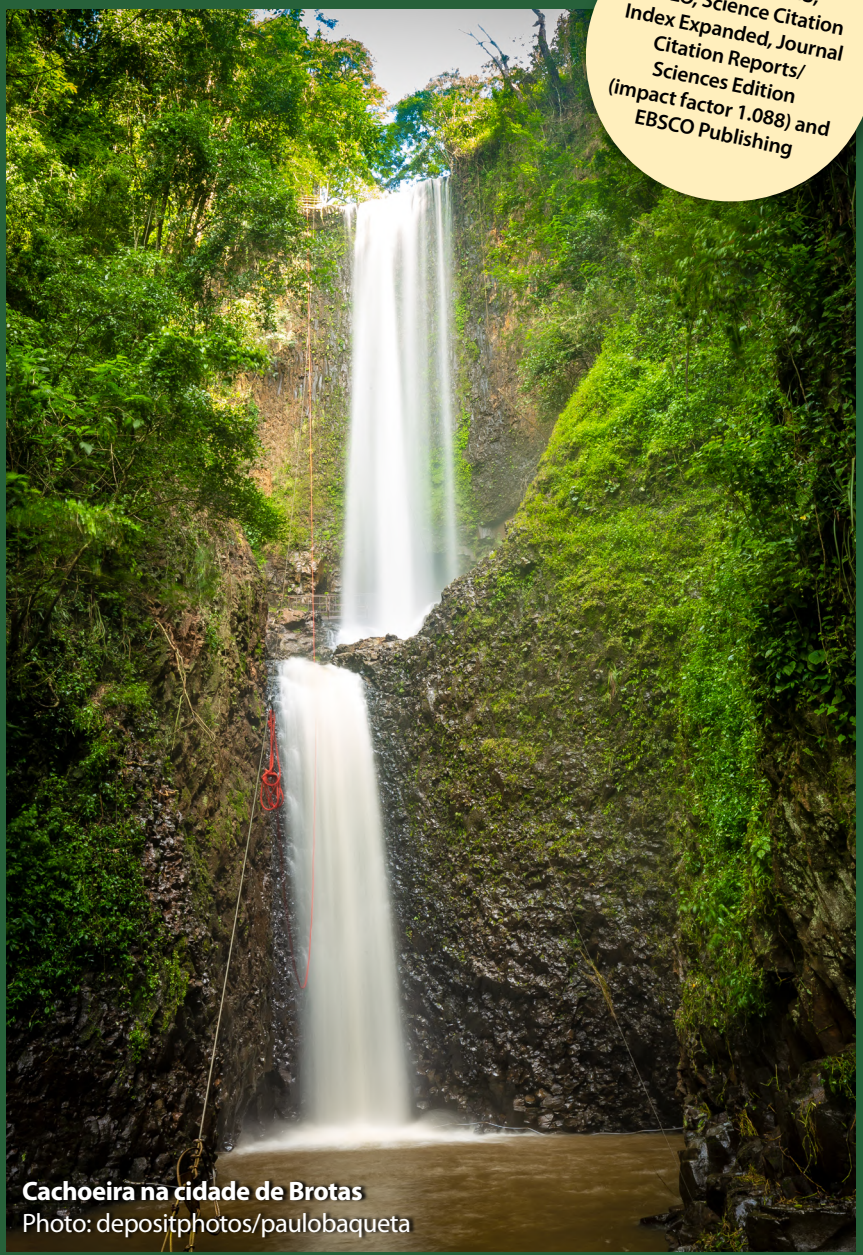

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COVID-19: better trustworthiness of clinical evidence through clinical trials and systematic reviews

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Recently, two major medical journals, The Lancet and New England Journal of Medicine, each withdrew an article on coronavirus from their databases[1] and the World Health Organization (WHO) cancelled and restarted a clinical trial on the use of hydroxychloroquine for treating the COVID-19 disease. Soon afterwards, the WHO stated that the possibility of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by asymptomatic individuals would only be rare, but then quickly denied what had been declared.

Announcements of cures for COVID-19 are appearing frequently. However, there is a clear simultaneous association between such news and the share values of drug-manufacturing laboratories that are promising miraculous cures on the basis of just a few cases that were poorly or barely documented.

It seems that the virus is also affecting the health sciences, the reputations of renowned journals, the state of political debate and the institutions responsible for preserving the population's state of physical, mental and social wellbeing, i.e. people's health.

All of this is easy to understand given the gravity of the tragic context. Moreover, it has occurred because clinical research not only requires clinical competence but also needs great detachment, time, impartiality and good evidence (proof) coming from other careful research.

Healthcare practices and evidence-based medicine require the use of reasoning. However, we need to be prepared not only to use rational thinking but also to avoid situations in which interests, emotions, fantasies, charlatanism and so on might get in the way of rationality and free scientific thought. Through this, professional practice can be based on good evidence, i.e. valid scientific proof, that interventions will have a higher chance of providing more benefit than harm.

For more than 30 years, together with many colleagues, we have striven to improve research, teaching and application of evidence-based medicine in Brazil and internationally. The results have been satisfying, because teaching and research within evidence-based medicine has had clear scientific, didactic, economic and juridical impacts, both in Brazil and around the world, over these last decades.

The thirst and respect for scientific evidence seen among many journalists in Brazil during this pandemic has been remarkable. It shows that our continuous collective work over this 35-year period has been worthwhile.

The charlatans who always appear at times of despair have had short lives with their vested-interest fake news, thanks to the now-established cultural foundation of demand for valid scientific evidence, coming from many different sectors of society.

Judicialization of healthcare in Brazil, in which judges have been asked to make rulings in cases based on emotional blackmail, for expensive treatments without proof of effectiveness to be released, under the justification that "without this, the patient will die", has largely been rationalized, with major savings of public expenditure. This has occurred through requirements for good evidence of effectiveness, efficiency and safety to be presented before permission for these therapies to be released through judicial petitions is granted. In this manner, the groundbreaking concept of evidence-based rights to healthcare has been created in Brazil. In this regard, we have trained around 3,000 judges, prosecutors and attorneys through distance-learning courses sponsored by the Brazilian Ministry of Health.

Unfortunately, for a variety of understandable reasons, the great pioneering experience of doctors in Wuhan, China, regarding COVID-19 could not be properly followed up with enough adequate clinical research methodologies, to generate valid proof, given the lack of time.

There was no time for good orchestration of scientific production that would properly take into account the basic principles for obtaining and evaluating valid evidence. It also has to be recognized that entire impact of this pandemic has been felt within a period of only six months. Most of the data have been retrospective.

A good clinical trial, with more than 1000 cases, would require several years of intense dedicated work. Cochrane systematic reviews take two to four years to be published. The Cochrane Collaboration is now promoting rapid reviews of lower sophistication on matters of urgent interest, within the fight against COVID-19.

If a new disease emerges, there is a need to know the following, for example:

- How to diagnose the disease
- What the clinical condition and its diagnostic tests are, and what usefulness and credibility the results from these tests have
- What the risk factors for individuals to become infected are
- What the risk factors for occurrences of severe outcomes are: for example, shock and kidney failure
- What the risk factors signaling severe forms of the disease and death are
- How to minimize complications of the disease, such as thromboembolism, cytokine storms, inflammatory reactions, acute respiratory insufficiency or kidney failure
- How to deal with the causes and consequence of the various complications

In all of this, the methodology of clinical epidemiology, which is the tool that generates the notions of evidence-based medicine and evidence-based health, is fundamental. Thus, to evaluate various risk factors, observational studies are extremely useful. These may include case-control studies, which can be applied to ascertain whether age, medications, profession or attitudes might have an association with becoming ill with the disease. These studies have the great advantage of enabling assessment of several risk factors in a single study and can be conducted quickly. A very good case-control study was published recently.[2]

On the other hand, because these studies are retrospective, they have the disadvantage of depending on the patients' memory. Moreover, they are not of much use for evaluating treatments and diagnostic tests because the proportions of cases and controls to be compared are established in an artificial manner.

For prospective evaluation of patients' evolution and what the risk factors associated with their evolution are, prospective cohort studies are fundamental. For example, it might be asked whether COVID-19 has outcomes of greater severity in patients whose laboratory assay results are more inclined to the left or to the right. In such cases, prospective studies that have been suitably designed beforehand will supply data and evidence that are much more trustworthy than those from retrospective analyses on cases that have already occurred but were not followed up in a planned manner. Prospective studies will thus avoid data losses.

It might be asked whether patients with higher C-reactive protein levels in blood analyses are at greater risk of mortality. Prospective cohort studies frequently have the disadvantage of requiring very long and laborious follow-ups. However, this does not occur significantly with COVID-19, given that this disease only lasts for two to four weeks. Thus, within a short time, large numbers of cases within this pandemic can be evaluated prospectively.

A variety of associations of risk factors for worsening of COVID-19, obtained through retrospective studies, have now been reported.[3,4] However, the strength of the evidence would be much more trustworthy if these data were obtained prospectively.

After hypotheses have been raised retrospectively, knowledge can be improved through prospective studies, so as to have a much more realistic vision of what is happening with each marker. Thus, therapeutic interventions aimed towards each desirable outcome and/or a set of outcomes of interest can be planned.

Therapeutic interventions cannot be securely assessed through case series without a protocol for a controlled clinical trial. Furthermore, such trials should preferably be double-blind, and these are necessarily prospective. Even though many people are greatly attracted towards cases series, these should generally serve only to generate questions that later on need to be answered using clinical trials. Hypotheses are then tested so that treatments can be put into practice based on evidence. This is very different from conduct based only on hypotheses.

Retrospective studies or studies without control groups may show that a series of patients received a benefit, or even some harm. However, these studies always leave a trail of continuing uncertainties if they are not followed by adequate prospective studies. This is so even in situations of the best of intentions, such as in cases of compassionate treatment. We end up not knowing whether the treatment was beneficial or harmful because we did not have a comparison group that was chosen randomly and impartially.

On the other hand, a clinical trial that is conducted with the competence and seriousness that this merits will, independent of the result, bring great benefits for all of humanity. In other words: if the intervention was beneficial, it can be used; but if it was ineffective, resources and sometimes lives will not be wasted, and the way forward may then be to explore new possibilities.

Among the sources of great confusion in the literature on this subject, both in academic settings and in the lay press, lack

of verification of the application of basic scientific fundaments of knowledge has generated confusion, conflict and commotion that can only be resolved through good-quality evidence.

For example, since the expected average mortality rate from symptomatic cases of COVID-19 is around 5%, it can be expected therefore that out of every 100 cases, around 95 should survive purely through the action of nature. Hence, even if only placebo is administered (which could be physiological serum or whatever else), 95% of the patients will be saved and will be computed as cases of successful treatment and the other 5% will not be able to come back to complain, in the remote hypothesis that all the cases are well documented.

Thus, in the absence of an adequate control group, masking for the researcher and patients, randomization, a good study protocol and a good way of conducting the study, large quantities of useless data end up supporting spurious opinions of well-intentioned people who are unaware of the appropriate methods for obtaining trustworthy data. This also supports the opinions of ill-intentioned people whose interest lies in deceiving others and promoting themselves professionally to gain financial advantages. Good scientific products are the fruit of a continuous struggle against possible confounding factors, systematic errors and random effects that might falsify the conclusions and mislead the researcher.

Although evidence-based medicine has led to great achievements so far, both in Brazil and around the world, there is still much to be done. The current pandemic has certainly helped to improve social awareness of the role of well-prepared scientists as essential actors in the war against this extremely dangerous invisible enemy. This is a war in which the lives of hundreds of millions of people depend on the outcome, and definitively it is not for just any healthcare professional to engage in.

On the websites of clinical trial registers, more than one hundred trials on treatments for COVID-19 are currently in progress. One of the best of these, Recovery, conducted by Oxford University,[5] is a factorial study, i.e. with several therapeutic interventions against COVID-19 in comparison with a control group. Its aim is to produce rapid answers to the research questions, which is possible because of the enormous number of cases that have occurred and the short duration of the disease.

One of these clinical trials has compared use of oral or intravenous dexamethasone in patients hospitalized with COVID-19 who require noninvasive oxygenation or mechanical ventilation. Given the high quality of this project and the adequate sample size, there is little doubt that this trial provides the first evidence of drug treatment with real benefit for treating patients with COVID-19 who require supplementary oxygenation, with significant reduction in mortality. However, this finding does not apply to milder cases.

Other studies with similar objectives are underway and, if their quality is good, their results may have an important role in reducing the remaining uncertainties, when added carefully to the current results in a conservative statistical process and through a properly done meta-analysis. In this manner, the best level of evidence for basing healthcare decisions on will be achieved through systematic reviews, and these trials will then enter history. The Cochrane Collaboration has the role of doing analyses of this nature in an impartial and live manner, i.e. continuously and explicitly, in all important fields of healthcare, and publishing them in the Cochrane Library.

Consulting good sources of evidence is essential for patients, students, doctors, other healthcare professionals, researchers, managers, journalists and lawyers. Free access to the Cochrane Library has been available in Brazil since 2001.

The Cochrane Center of Brazil has been in operation within the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP) since 1996 (https://brazil.cochrane.org/).

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Some lessons from the COVID-19 pandemic virus

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When the spread of the infection caused by the new coronavirus named COVID-19 was officially declared by the World Health Organization (WHO) to be a pandemic, the first idea was that it was just another respiratory disease related to a new virus strain; just another flu-like syndrome. The clinical presentation would have a classical spectrum ranging from asymptomatic infection to a respiratory distress syndrome needing respiratory support in intensive care units in the most severe cases. Therefore, the idea was that the impact of the virus would be restricted to the upper and lower respiratory system.

The development of the pandemic has shown us the real face of the virus. It is more complex and more particular than was expected by healthcare professionals and stakeholders. That was the first lesson that the virus has given to us.

The symptoms of the infection have multiple facets and it is not simple to fight against it. First, the key receptors enabling entry for the virus are angiotensin-converting enzyme 2 (ACE2) receptors, which have a strong relationship with blood pressure homeostasis through the renin-angiotensin-aldosterone system.[1] At the same time, the descriptions of the Wuhan series of cases have been showing that people with a previous diagnosis of hypertension presented an unexpectedly high risk of development of severe cases of COVID-19. Moreover, the virus has been found to have direct action at the endothelial level, thus indicating that the infection could be acting on unstable atherosclerotic plaques in the coronary artery bed, and hence increasing the risk of sudden cardiac death, myocardial infarction and decompensated heart failure.[2,3]

Moreover, the infection has been found to be associated with thrombosis and thromboembolic episodes, not only in the lungs but also in relation to stroke and other venous and arterial thromboembolic complications with a high risk of death.[4,5] Regarding stroke, large-vessel stroke has been described as a presenting feature of COVID-19 in young adults.[6] Other complications that have been reported include septic and cardiovascular shock,[7] especially in people with a history of comorbidities;[8] and also alterations in kidney function. Unusual presentations, such as mesenteric thrombosis and acute thyroiditis, among others, need further investigation.

The second lesson from COVID-19 is that the relationship between humankind and the surrounding environment needs to undergo changes, urgently. Most of the more recent pandemics have probably arisen as the consequence of an unhealthy relationship between humans and wild animals and livestock.

We are constantly invading the space of other living animals. This is not new. We have forgotten, in the history of other diseases, that many of them came from animals that humans have domesticated, starting in the Neolithic age, more than 10,000 years ago. The agricultural era emerged accompanied by domestication of wild animals. Influenza originated from pigs and chicken; common cold was brought by horses; tuberculosis from cattle; and Lyme disease from infected ticks that live mostly in deer.[9] More recently, AIDS originated from chimpanzees; SARS coronavirus probably from civets and Asian raccoon dogs (*Nyctereutes procyonoides*),[10] swine influenza (H1N1) from pigs[11] and Spanish influenza probably also from pigs.[12]

Another lesson that we need to understand is that no city and no country is prepared to care for so many patients that need ventilatory support at the same time. One of richest cities in the world, New York, has had to accept the limitations of its healthcare system in this situation. However, it is important to state that the burden of the disease will be greater in low to

middle-income countries with their overloaded healthcare systems and high numbers of people living in poor communities. In addition, one fact is clear: Asian countries have been more successful in dealing with COVID-19 than most Western countries.[13]

The COVID-19 pandemic will not end with the discharge of the last patients in whichever place in the world where this occurs. Patients who have stayed in an intensive care unit for many weeks will need rehabilitation, physiotherapy and speech therapy, and probably mental health support after discharge. The real impact of the pandemic on mental health is not known at this point in time.

The pandemic has changed the way in which people die. Patients have mostly died alone, far from their families. This is and will be a great burden for these families that lost relatives without the proper rites of passage, such as the viewing and funeral ceremonies. Most families are not given the chance to give a proper farewell to beloved relatives and friends. It is important to think about this. Moreover, COVID-19 is just the most recent pandemic: it is unlikely to be the last one.

We need to become prepared for new pandemics and to create new scientific protocols and rites of passage to deal with all the biological and spiritual consequences of this disease that has devastated so many countries in 2020, a year that we will not forget. We need to learn from this and seek new solutions to deal with future pandemics.

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The brief psychotherapeutic intervention "relaxation, mental images and spirituality": a systematic review

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Psychosomatic medicine.
Palliative care.

AUTHORS' KEY WORDS:
Complementary medicine.
Alternative therapies.
Guided images.
Directed imagination.
Visualization.

ABSTRACT

BACKGROUND: The brief psychotherapeutic intervention "relaxation, mental images and spirituality" (relaxamento, imagens mentais e espiritualidade, RIME) is a form of complementary and alternative health-related therapy. It is a pioneer in the matter of relating the elements of spirituality to relaxation and to visualization of mental images.

OBJECTIVE: To ascertain the history, use and benefits of RIME that have been reported in the scientific literature, within different health/disease contexts. The questions that guided this study were: In what contexts has the brief RIME psychotherapeutic intervention been used? What were its benefits?

DESIGN AND SETTING: Systematic review, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology, in a public university.

METHODS: The BVSPsi, CINAHL, MEDLINE, SciELO, SCOPUS and Web of Science databases were searched in September and October 2018.

RESULTS: The findings showed that RIME promoted resignification of the symbolic pain of the death of patients without the possibility of cure; improved quality of life within the process of dying; contributed to the quality of life of breast cancer patients with cure possibilities; contributed to the emotional wellbeing of ostomized patients; brought quality-of-life benefits for patients with head-and-neck cancer; promoted empowerment for women with breast cancer and strengthened their libido; and promoted resignification of the spiritual pain of bereaved youths, offering a satisfactory return from mourning preparation.

CONCLUSIONS: It was found that RIME has a construct history based on rigorous scientific methodology, covering quality of life and spiritual, emotional and subjective wellbeing. RIME has not been used internationally and new studies within this field, with different cases, should be encouraged.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO ID 164211.

INTRODUCTION

High levels of stress lead to problems that compromise health, quality of life and individual productivity and consequently act to trigger diseases. These problems are some of the reasons that have led to research on methods for minimizing the harmful effects of stress.[1]

Integrative and complementary practices, also known as traditional and complementary medicines, are a set of healthcare practices that encompass the traditions of care practiced in different cultures and other complementary practices that are not included in those traditions, but are incorporated into the healthcare system.[2] These practices are characterized by procedures that have the aim of producing psychophysical and logical relaxation, and they involve creation of therapeutic bonds and integration of individuals with their environment.[2]

In a randomized clinical trial on 60 patients with chronic kidney disease in which the objective was to evaluate the therapeutic effect of music on the anxiety and vital parameters of those patients, the results showed that music therapy, which is one of the integrative and complementary practices that have recently been introduced into the Brazilian National Health System (Sistema Único de Saúde, SUS), significantly reduced their anxiety.[3]

Through integrating techniques of relaxation, directed imagination and elements that make up spirituality, a brief intervention named "relaxation, mental images and spirituality" (relaxamento, imagens mentais e espiritualidade, RIME) was developed. RIME is a form of complementary and alternative health therapy and is a pioneer in relating elements of spirituality to relaxation and to visualization of mental images.[4] In 2005, a training program was developed for use of this intervention by other healthcare professionals, with analysis on these professionals'

experience during its application and evaluation among patients.[5] Since the time of this training experience, the technique has gained the abbreviation RIME and has begun to be considered to be a psychotherapeutic intervention.[5]

RIME is a brief psychotherapeutic intervention for terminally ill patients, and for patients with chronic diseases that have curative possibilities, within a palliative care context. The purpose of this intervention is to improve the patients' wellbeing, through stimulating positive transformations that come from within the individual.[6]

The resignification of spiritual pain through the RIME intervention integrates two techniques for addressing questions of spirituality: mental relaxation and visualization of mental images. The association of these two techniques favors deeper contact with individuals' internal and personal realities, which enables them to change their attitudes, conceive new ideas and elaborate new meanings, in the light of events.

As healthcare professionals, we can promote bringing these practices together for those who can benefit from them, especially for individuals who are physically and psychologically debilitated. Such actions form part of holistic humanization behavior.

The questions that guided this study were: In what contexts has the brief psychotherapeutic intervention "relaxation, mental imagery and spirituality" been used? What were its benefits?

OBJECTIVE

The purpose of this review was to ascertain the history, use and benefits of the RIME brief psychotherapeutic intervention that have been reported in the scientific literature in experimental or non-experimental studies within different health/disease contexts.

METHODS

Design and setting

The methodological design for this study consisted of a systematic review of the literature that was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology, as proposed by Moher et al.[7]

Search strategy

The searches were carried out in the following databases: BVSPsi, CINAHL, MEDLINE Complete, SciELO, SCOPUS and Web of Science. The descriptors were chosen and identified in accordance with the MeSH list of descriptors, as follows: *Relaxation, Mental Images* and *Spirituality.* Two combinations were performed, of which the first was: ("*Relaxation*" AND "*Mental Images*" AND "*Spirituality*"). The second combination was composed only of the intervention abbreviation: ("*RIME*"). The same search strategies were used in all databases (**Table 1**). This review was conducted in September and October 2018.

Eligibility selection criteria

Article identification and screening were guided by the following inclusion criteria: cross-sectional and experimental studies, which could either be randomized or not, using the RIME brief psychotherapeutic intervention method, in health/disease contexts; studies conducted on patients in any age group; patients with a probable diagnosis of any type of chronic or acute pathological condition, either in palliative care or not; studies that used the RIME intervention in association with assessment of other variables such as quality of life, resilience, wellbeing, spirituality and others; articles indexed in peer-reviewed journals; year of publication from 1999 onwards; written in the English, Spanish or Portuguese language; and full text available.

The manuscript selection was done independently and in a blinded manner by two researchers who analyzed the titles and abstracts. If these were found not to be related to the proposed theme, or not to fit the inclusion criteria, they were excluded. After this stage, a consensus meeting was held to resolve doubts and possible disagreements regarding the data collected, based on the PRISMA protocol.

RESULTS

A total of 102 studies were selected, through the search in the databases. From the first combination, ("*Relaxation*" AND "*Mental Images*" AND "*Spirituality*"), 20 articles were identified: BVSPsi = 1; CINAHL = 2; MEDLINE = 3; SciELO = 4; SCOPUS = 6; and Web of Science = 4. From the second combination, ("*RIME*"), 82 articles came up: BVSPsi = 6; CINAHL = 68; and SciELO = 8. Four additional articles were also selected from other sources, through Google Scholar, making an overall total of 106 articles.

As shown in **Figure 1**, 21 repeated articles were removed, thus leaving 85 titles and abstracts to read. After the various exclusions, 12 studies were selected to make up this review. However, three more articles were subsequently excluded, after reading them fully, because they were found to consist of

Table 1. Search strategies used in the databases BVSPsi, CINAHL, MEDLINE Complete, SciELO, SCOPUS and Web of Science

BVSPsi	1 "*Relaxation*" AND "*Mental Images*" AND "*Spirituality*" 2 "RIME"
CINAHL	1 "*Relaxation*" AND "*Mental Images*" AND "*Spirituality*" 2 "RIME"
MEDLINE Complete	1 "*Relaxation*" AND "*Mental Images*" AND "*Spirituality*" 2 "RIME"
SciELO	1 "*Relaxation*" AND "*Mental Images*" AND "*Spirituality*" 2 "RIME"
SCOPUS	1 "*Relaxation*" AND "*Mental Images*" AND "*Spirituality*" 2 "RIME"
Web of Science	1 "*Relaxation*" AND "*Mental Images*" AND "*Spirituality*" 2 "RIME"

abstracts indexed in congress annals. Hence, in the end, this review was conducted on nine studies.

The material identified in this review is summarized in **Table 2**. It consisted of seven articles, one master's degree thesis and one doctoral degree thesis. The two theses came from other sources (i.e. not the databases), as previously mentioned.[4,5,8,10-15]

DISCUSSION

In order to provide a detailed and uniform profile of the use of RIME, the studies will be approached sequentially, as shown in **Table 2**.

Elias and Giglio[4] studied the effectiveness of the RIME intervention for terminal patients. This was developed through integrating techniques for mental relaxation and visualization of mental images with the elements that make up spirituality, with the purpose of resignifying the symbolic pain of death, as represented by mental and spiritual pain. These authors investigated five adult women aged 37 to 75 years who had been diagnosed with breast cancer at a non-curable stage. One putative variant that was studied was quality of life, and the intervention variables were "mental pain", represented by humor, fear, "depressive" ideas and death; and ideas and conceptions regarding spirituality, the meaning of life and death and God.

These authors followed the steps of identification of the symbolic pain of death through a semi-structured interview, in which the elements of mental and spiritual pain, mental relaxation techniques and visualization of mental image orientation were condensed. It was observed that it was possible to obtain good results through applying the methods of mental relaxation, mental imagery and spirituality during the period that followed the phase of moving beyond the possibility of cure. The integration of relaxation techniques, visualization of mental images and elements that composed spirituality was important for resignifying the symbolic pain of the death of patients who were beyond the possibility of cure.

Based on reports from patients who had undergone a near-death experience that suggested an occurrence of transcendence, Elias[8] developed the RIME intervention pilot project in 1988. The study was conducted on four children and three adolescents aged 22 months to 17 years, all with cancer and without the possibility of cure. A mental image visualization technique was developed among these children through the instruments of graphic activities, games and children's stories; and among these adolescents, through young-adult and youth stories and films (with a plot containing a symbolic relationship with the patient's mental and spiritual pain) and through visualization itself.

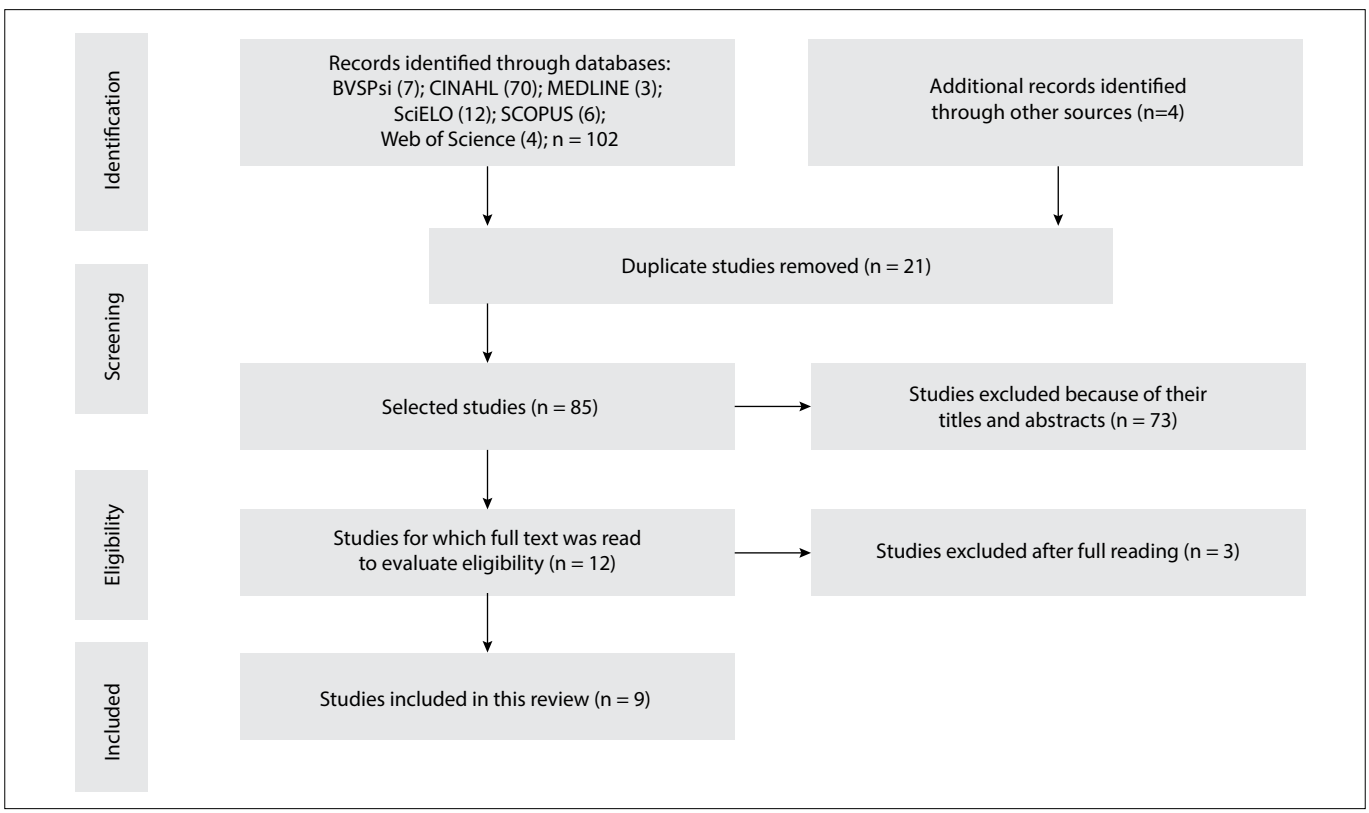

Figure 1. Article selection and identification process.

Elias[8] observed that this proposed method, i.e. integration of the techniques of mental relaxation and mental image visualization with the elements that make up spirituality, favored resignifying the symbolic pain of death among the seven patients, since all of them would now go on to die with moral dignity, in a state of emotional support and in peace. It was concluded that the proposed method provided quality of life within the process of dying, thus enabling a serene and dignified death.

In this study (Elias[8]), in comparing follow-ups performed among adolescents and children who were within the process of dying, it was observed that the adolescents facing the symbolic pain of death presented both mental and spiritual pain, but the children presented only mental pain, represented by a depressive mood that was linked to anxiety about separation. This difference was attributed to these children's cognitive stage.

On the basis of Piaget's studies, Elkind[9] stated that children from two to seven years old are in the preoperational thinking stage, whereas from seven to eleven years of age they are at the stage of concrete operational thinking. This would mean that children at all of these ages (two to eleven years) have not yet developed the ability to think abstractly. Such thinking is necessary in order to feel fear of death and the time after death, and to develop ideas and conceptions relating to spirituality.

Between 2002 and 2005, while researching for a doctoral degree thesis, Elias developed a training course to instruct healthcare professionals about the use of the RIME intervention. This was described by Elias et al.[5] using qualitative methodology, phenomenology and action research as the theoretical bases. The training course was put into operation for use in interventions and the experience of these professionals during its application and evaluation among patients was analyzed. Six professionals participated in the study: a nurse, a doctor, three psychologists and an alternative therapist. All of them had qualifications relating to palliative care. These professionals were invited to apply the intervention to 11 cancer patients aged 27 to 76 years, who were either in public hospitals and in their homes, in the cities of Campinas, Piracicaba and São Paulo in Brazil. From this training, the technique gained the abbreviation RIME and began to be considered to be a brief psychotherapeutic intervention.

Table 2. Summary of studies selected for this review

Author/year	Study location	Design	n	Age	Main findings
Elias et al.[4]	Campinas (SP)	Qualitative approach - clinical case study, longitudinal	5	37-75 years	Cancer patients who received two to four relaxation, mental image and spirituality sessions achieved better quality of life within the process of dying. It was observed that application of this technique was important for resignification of the symbolic pain of these patients' deaths.
Elias[8]	Campinas (SP)	Qualitative approach	7	From 22 months to 17 years	In a qualitative study, four children and three adolescents with cancer that was beyond the possibilities of cure, each received three to ten sessions of relaxation, mental images and spirituality. After the visits, it was observed that the intervention gave new meaning to the symbolic pain of death and provided quality of life within the process of dying for these patients.
Elias et al. [5]	Campinas (SP)	Qualitative/ quantitative	6	**	Development of a training course to instruct healthcare professionals about the use of RIME intervention. Qualitative results were analyzed through content analysis, semi-structured interviews and a diary; the quantitative data were analyzed through a descriptive method, using the Wilcoxon test. The program proved to be effective in preparing healthcare professionals to using RIME intervention, enabling them to care and to provide spiritual assistance from an academic perspective.
Elias et al.[10]	Campinas (SP)	Quantitative/ qualitative	11	27-76 years	A study conducted among cancer patients who received RIME intervention. Through a qualitative approach, six categories and eleven subcategories were found, among which the most prevalent were: fear of death due to denial of the severity of the clinical picture; fear of death due to perceiving the severity of the clinical picture; and fear of disintegration of feeling and of being affectively forgotten after death. Through a quantitative analysis, a statistically significant difference was observed ($P < 0.0001$). The results suggested that RIME promoted quality of life within the process of dying, with serenity and dignity before death.

Continue....

Table 2. Summary of studies selected for this review

Author/year	Study location	Design	n	Age	Main findings
Ribeiro et al.[11]	São Paulo (SP)	Quantitative/ qualitative	21	61.3 years*	Patients using intestinal ostomies during an immediate postoperative period marked a visual analogue scale regarding wellbeing before and after RIME application: the respective mean scores were 3.33 and 1.38. Through asking the patients how they felt emotionally before the surgery and after the RIME intervention, the following context units emerged: feelings, emotions, sensations and expectations of action, which generated four distinct categories that represented the transformation relating to mental wellbeing. RIME was the only variable that presented statistical significance, which led to the affirmation that it contributed to improvement of the patients' emotional wellbeing.
Elias et al.[12]	São Paulo (SP)	Randomized controlled study/quantitative/ qualitative	28	33-59 years	The women were screened and randomized through five draw groups. In each group, half of the patients went to the control group to receive up to twelve sessions of brief psychotherapy (BP) and the other half went to the RIME group to receive three sessions of this plus twelve BP sessions. The qualitative data were treated using branched content analysis into thematic analysis; the quantitative data were collected using the WHOQOL brief scale, Rosenberg's self-esteem scale, Beck's hopelessness scale and a visual analogue wellbeing scale. The results showed that RIME promoted a significant improvement in quality of life perception (38.3%), compared with the control group (12.5%), along with a significant improvement in the patients' self-esteem (14.6%).
Espinha[13]	Marília (SP)	Randomized controlled study	44	57-63 years	A study conducted among patients with head-and-neck cancer, using the performance scale instrument (ECOG) the QOL questionnaire EORTC-QLQ-C30 and the QLQ-H&N35 questionnaire for patients with head-and-neck neoplasia. The results suggested that the RIME intervention led to quality-of-life benefits for patients with head-and-neck cancer, regardless of the toxicity of the radiotherapy treatment.
Elias et al.[14]	São Paulo (SP)	Comparative exploratory, quantitative/qualitative approach	28	33-59 years	Implementation of the RIME brief psychotherapeutic intervention among women with breast cancer who were undergoing treatment, with the possibility of cure. The main focus of the study was to present the qualitative results, for which the instruments used were recorded semi-structured interviews and graphic representations from before the first and after the third RIME session. The results showed that RIME promoted empowerment for higher libido and constructive strength among women with breast cancer with the potential for cure.
Pereira[15]	Fortaleza (CE)	Qualitative research	4	16-17 years	The RIME intervention was used to resignify the pain of symbolic loss among four adolescents who were in a context of vulnerability. The analysis from the RIME brief psychotherapeutic intervention was done through observation of the spiritual pain and its intensity, as manifested by the research subjects, along with their experiences of pain resignification. For this, two instruments were used: a visual analogue scale of wellbeing and content analysis through the thematic analysis technique. The RIME intervention promoted resignification of the spiritual pain of these young mourners, thus offering a satisfactory return from mourning and providing possibilities for working to break ties and recurrence of pain.

*Average age; **unspecified age.

RIME = relaxation, mental images and spirituality (relaxamento, imagens mentais e espiritualidade); WHOQOL = World Health Organization Quality of Life; ECOG = Eastern Cooperative Oncology Group; QOL = Quality of Life; EORTC = European Organization for Research and Treatment of Cancer.

Administration of RIME revealed statistically significant differences in wellbeing levels. The patients reported having higher wellbeing levels at the end of the sessions than at the beginning ($P < 0.0001$), thus suggesting that RIME led to resignification of spiritual pain for these terminal patients. The proposed training program proved to be effective for preparing healthcare professionals to implement RIME interventions, both for taking care of such patients and for providing spiritual assistance from an academic perspective.[5]

Elias, Giglio & Pimenta[10] conducted a qualitative study based on phenomenology and quantitative descriptions, in which the aim was to study the nature of spiritual pain and its resignification during application of RIME interventions. The sample consisted of 11 patients with final-stage cancer that was being treated in public hospitals, by six professionals who had been trained to apply RIME. The most prevalent categories of feelings were the following: fear of death due to the individual's denial of the severity of his or her clinical state (n = 5); fear of death due to perceiving the severity of the clinical picture (n = 5); and fear that after death there would be disintegration of feeling, non-existence and being affectively forgotten (n = 5). These results suggested that RIME promoted quality of life during the process of dying, with serenity and dignity before death.

Ribeiro et al.[11] conducted a qualitative study in which they aimed to evaluate and discuss the efficacy of the RIME brief psychotherapeutic intervention for wellbeing, in a group of patients who were using intestinal ostomies during a postoperative period. Twenty-one patients participated in the sample and were assessed regarding their wellbeing using a visual analogue scale before and after RIME application. Their mean scores were 3.33 before and 1.38 after the intervention. From asking these patients how they felt emotionally before the surgery and after the RIME intervention, the following context units were extracted: feelings, emotions, sensations and expectations of action. These generated four distinct categories that represented the transformation relating to mental wellbeing. It was concluded that RIME was the only variable that presented statistical significance, which led to affirmation that it contributed towards improving these ostomized patients' emotional wellbeing.

Elias et al.[12] conducted a study with the objective of ascertaining the benefits from RIME among 28 women who had been diagnosed with breast cancer with the possibility of cure. They had been mastectomized and were in the process of breast reconstruction with adjuvant treatments. These women were screened and randomized through five draw groups, and in each group, half of the patients went to the control group to receive up to twelve sessions of brief psychotherapy (BP) and the other half went to the RIME group to receive three sessions of this plus twelve BP sessions.

From the statistical analysis comparing the RIME group with the control group, a significant improvement (38.3%) in quality-of-life perception on the World Health Organization Quality of Life (WHOQOL) scale after RIME, compared with BP alone in the control group (12.5%), and with BP in the RIME group (16.2%). There was a significant improvement in self-esteem after RIME (14.6%), compared with BP alone in both the control group (worsened by 35.9%) and BP in the RIME group (8.3%). There were similar improvements regarding hopelessness in the RIME group and in the control group: RIME = 20.1%; RIME + BP = 27.1%; and BP = 11.1%. There was significant improvement in wellbeing relating to focused distress (measured using a visual analogue scale), both in the RIME group (poor wellbeing to wellbeing) and in the control group (very poor wellbeing to good wellbeing). None of the three treatments (RIME, RIME + BP or BP) showed any significant improvement in the WHOQOL domains or in WHOQOL health satisfaction.[12]

In another randomized controlled clinical study,[13] conducted in Marília, state of São Paulo, the aim was to evaluate the efficacy of the RIME brief psychotherapeutic intervention among 44 patients with head-and-neck cancer, in relation to physical symptoms and quality-of-life levels. Patients in the control group only received the standard support treatment that was routinely used in that hospital unit for patients with head-and-neck cancer.

All the participants underwent performance status measurements using the Eastern Cooperative Oncology Group (ECOG) scale. They answered a questionnaire regarding their profile and, at both the start and the end of the study period, answered questions relating to the quality-of-life evaluation of the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (EORTC-QLQ-C30) and the EORTC-QLQ-H&N35 questionnaire. The QLQ-H&N35 (Quality-of-Life Questionnaire "Head-and-Neck Module" 35 items) questionnaire is a specific module of the EORTC-QLQ-C30 that is intended for patients with head-and-neck neoplasms, at various stages and undergoing different treatments.

In addition to support treatment, the experimental group underwent the RIME therapeutic intervention periodically. In the intervention group, subjects who underwent RIME showed significant improvements in most domains of the general and specific quality-of-life scales at the end of the radiotherapy treatment. Furthermore, there was lower consumption of analgesic drugs and less weight reduction at the end of the treatment. The results suggested that the RIME brief psychotherapeutic intervention provided quality-of-life benefits for patients with head-and-neck cancer, regardless of the toxicity that resulted from the radiotherapy treatment.

Elias et al.[14] conducted a randomized study on implementation of RIME for women undergoing breast cancer treatment, with the possibility of cure. The main focus of this study was to present qualitative results from recorded semi-structured interviews and graphic representations that were conducted before the first and after the third RIME session.

Qualitative analysis on these data indicated that the main issue among the women with breast cancer in the RIME group, i.e. the focus for transformation, was the need for self-valorization. This was also observed in the BP control group. The main psychological transformations mediated by the RIME symbolic elements were the following:

1. transformation of female absence or dissipation to loving or protective representation;
2. transformation of masculine intangibles, absence or impotence to tangible, powerful and loving representation; and
3. transformation of divine intangibles that are inaccessible or impersonal to close-at-hand, accessible and loving representation.

In a qualitative study, conducted in Fortaleza, state of Ceará, Pereira[15] used RIME interventions in order to resignify losses caused by deaths. In this study, a psychopedagogical device that would resignify the spiritual pain of loss was proposed, in order to help four young mourners deal with the deaths of people for whom they had affectionate ties who had been lost through acts of violence. The four individuals studied were school-age adolescents aged between 16 and 17 years who were living in a region of extremely high vulnerability, where deaths occur very frequently, mainly through violence.

This author took mourning to be a reactive psychological process that constituted an adaptation to rupturing of bonds, and considered that the bereaved individual would be an active subject in the processes of facing up to ruptures and losses. Thus, this author chose life history and training and the RIME intervention as the research method. Through integrating these two forms of access, with formative and transformational self-knowledge, the results showed that even if the rupturing of a bond through death provokes inevitable pain, it can be resignified to acquire a providing sense: new ways of living, loving and dealing with finitude.

Each of these adolescents received three sessions of the intervention, which was applied once a week. RIME was used with the aim of resignifying the symbolic pain of the loss suffered by these four adolescents, in their context of vulnerability. The analysis on the results from the RIME brief psychotherapeutic intervention was made through observation of the spiritual pain and its intensity that the study subjects manifested, along with their experiences of resignification of this pain. For this, two instruments were used: a visual analogue scale of wellbeing and content analysis through a thematic analysis technique.

In specific relation to the RIME intervention, this promoted resignification of the spiritual pain of the bereaved young people, thus offering a satisfactory return from mourning and providing possibilities for working on the rupturing of ties and the recurrent pain from these ties.[15]

CONCLUSIONS

It was found that RIME has a construct history based on rigorous scientific methodology, and that it has become consolidated from the time of its creation to the present day, including n relation to quality of life and emotional and subjective wellbeing, in different health-disease contexts.

The pathological conditions that have been studied using this method have included patients with breast cancer who were beyond the curable stage; patients with other types of cancers, both beyond and within the possibilities for cure; patients using intestinal ostomies during an immediate postoperative period; and patients with head-and-neck cancer. This intervention has also been applied to bereaved adolescents within a context of vulnerability, who needed to elaborate resignification of spiritual pain and to work on the rupturing of bonds and the pain arising from this.

The RIME brief psychotherapeutic intervention promoted resignification of the symbolic pain of death among patients who were beyond the possibility of cure; improved quality of life within the process of dying; and contributed towards improve emotional wellbeing among ostomy patients. It provided quality-of-life benefits for patients with head-and-neck cancer, regardless of the toxicity of radiotherapy treatment. It promoted empowerment for strengthening libido and constructive force among women with breast cancer for whom cure was possible, and promoted resignification of the bereavement of young men in spiritual pain.

The RIME intervention provides a major contribution to science and the humanization of healthcare. One limitation identified in the present study was that we found that this intervention has not yet been used internationally. New studies within this field, covering different cases, should therefore be encouraged.

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Detecting the extent of control over selection bias relating to oral health and otorhinolaryngology: cross-sectional study

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ABSTRACT

BACKGROUND: The authors of randomized controlled trials will usually claim that they have met the randomization process criterion. However, sequence generation schemes differ and some schemes that are claimed to be randomized are not genuinely randomized. Even less well understood, and often more difficult to ascertain, is whether the allocation was really concealed.

OBJECTIVE: To detect the extent of control over selection bias, in a comparison between two Cochrane groups: oral health and otorhinolaryngology; and to describe the methods used to control for this bias.

DESIGN AND SETTING: Cross-sectional study conducted in a public university in São Paulo, Brazil.

METHODS: The risk of selection bias in 1,714 records indexed in Medline database up to 2018 was assessed, independent of language and access. Two dimensions implicated in the allocation were considered: generation of the allocation sequence; and allocation concealment.

RESULTS: We included 420 randomized controlled trials and all of them were evaluated to detect selection bias. In the sample studied, only 28 properly controlled the selection bias. Lack of control over selection bias was present in 80% of the studies evaluated in both groups.

CONCLUSION: The two groups were similar regarding control over selection bias. They are also similar to the methods used. The dimension of allocation concealment appears to be a limiting factor with regard to production of randomized controlled trials with low risk of selection bias. The quality of reporting in studies on oral health and otorhinolaryngology is suboptimal and needs to be improved, in line with other fields of healthcare.

INTRODUCTION

Randomized controlled trials (RCTs) are considered to be a powerful research design for evaluating the effects of healthcare interventions. They constituted one of the most important scientific advances during the 20th century. Through using such trials, researchers have the assurance that the differences found between the groups evaluated truly result from the effectiveness of the intervention, given that the allocation is random, i.e. there is an equal distribution of prognoses between the groups.[1-3]

The controls over the allocation implementation process include generation of a random allocation sequence and simultaneous allocation concealment.[4,5] It is fundamentally important that the investigators should not be capable of anticipating the allocation of the next participants. Absence of controls over the allocation process is a major barrier to internal validity, because this allows the researcher to predict the participants' allocation at the recruitment stage. Even when bias signals are minimal, systematic differences in prognosis can be expected between the groups that will be compared. In particular, selection bias may compromise any randomized experiment in which the enrollment of subjects is sequential and the administration of treatments is unmasked.[6-9]

The authors of RCTs will usually claim that they have met the randomization process criterion, in the title of the article or in the abstract. However, sequence generation schemes differ, and some schemes that are claimed to be randomized are not genuinely randomized.[10-13]

Even less well understood, and often more difficult to ascertain, is whether the allocation was really concealed. Allocation concealment is actually part of the randomization process and, while distinct from the method used to generate the randomized sequence, is essential to the success of randomization.[13-15]

The idea of comparing data from different fields within healthcare is not new.[16-18] However, today, there is a tendency for each research group only to evaluate data from their own field.[19-38] True randomized controlled trials allow healthcare providers to make informed inferences about the validity of these trials.

OBJECTIVE

The aims of this study were to detect the extent of control over selection bias through comparing different fields within healthcare: otorhinolaryngology and oral health; and to describe the methods used to control for this bias.

METHODS

This was a cross-sectional study in which the risk of selection bias of randomized controlled trials indexed in the Medline database was assessed.

Primary studies with an RCT design in the fields of otorhinolaryngology (i.e. ear, nose and throat (ENT) diseases) and oral healthcare that were published in journals and indexed in the Medline database were eligible, independent of language and access. A random sample was taken from these studies. These two fields of healthcare were chosen because of the similar numbers of Cochrane systematic reviews that have been published, for reasons of their anatomical and functional proximity and because they share healthcare problems.

Since it was not possible to conduct a cohort study to evaluate the methods of randomized controlled trials, we chose to conduct two cross-over studies at two different time points: 2011-2013 and 2018-2020. Data from this second period have already begun to be collected and as soon as finalized will be compared and published. Thus, initially, approximately 755 potential RCTs in the oral health group and 959 potential RCTs in the ENT group were retrieved.

Sample size

The sample calculation was performed taking a margin of error of 5%, a difference between groups of 30% and a confidence interval of 95%, in the light of our working hypothesis. It was found that analysis on approximately 200 articles in each field would be necessary. A total of 420 RCTs were included, comprising 214 on ENT and 206 on oral health.

Types of data and methods (variables and bias)

To evaluate the allocation process, the Cochrane Collaboration risk-of-bias tool was used.[9] Two dimensions implicated in the allocation were considered: generation of the allocation sequence; and allocation concealment.

The variable "risk of bias" was segmented into three possible responses: a) low risk of bias, meaning that the author controlled the entire allocation process, comprising random generation and allocation concealment, and therefore that this was an RCT with low risk of selection bias; b) uncertain risk of bias, meaning that the author did not report the allocation process comprising random generation and concealment of the allocation, or reported it in such a way that it was impossible to know for sure what the real situation of the allocation and concealment was; and c) high risk of bias, meaning that the author reported using an incorrect method for the allocation process.

Search methods for identifying studies (data sources)

To identify RCTs in the ENT group, an electronic search strategy recommended by the Cochrane Ear, Nose and Throat Disorders Group was used, with the following search terms: ear nose throat; general ENT and head-and-neck cancer; nose and adenoids, pharynx, larynx and upper respiratory tract infection (URTI); salivary glands; and skull base and neck. This was combined with the Cochrane highly sensitive search strategies for identifying randomized trials in Medline (**Figure 1**). The same approach was used for identifying RCTs in the oral health group (**Figure 1**).

Data extraction and management

To assess the risk of the RCTs, two independent reviewers classified the studies, to ensure that these trials could be replicated. The first was a medical researcher (CAF) who was an expert on methodology; and the second was a pharmacist who was an expert on epidemiology (VA). Disagreements were discussed with a third researcher, who was an expert on methodology, to establish a consensus (CASL).

Statistical processing of data

The statistical analyses were performed using the SPSS 19.0 software for Windows. The variable "risk of bias" was taken to be the

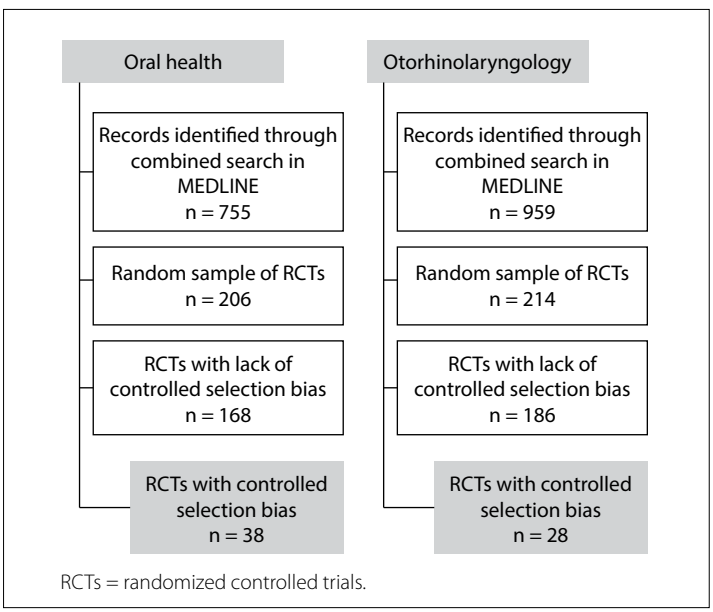

Figure 1. Flowchart of search.

ordinal and each group was taken to be the categorical variable. To ascertain differences between the groups within each dimension of the risk of bias, nonparametric test were used (Pearson chi-square and Mantel-Haenszel). The odds ratio (OR) was used to represent the chances between the groups evaluated. The significance level used in the tests was 5% (alpha = 0.05), and tests with P-values less than 5% ($P < 0.05$) were taken to be statistically significant.

RESULTS

The Cochrane strategy combined with the key words in the field of oral health recovered 755 records. From this universe, a sample of 206 RCTs was taken. All of these RCTs were evaluated to detect selection bias. In the sample studied, only 38 RCTs properly controlled selection bias (**Figure 1**).

The Cochrane strategy combined with the key words in the field of ENT recovered 959 records. From this universe, a sample of 214 RCTs was taken. All of these RCTs were evaluated to detect selection bias. In the sample studied, only 28 RCTs properly controlled selection bias (**Figure 1**).

The level of agreement between the reviewers was measured using the kappa statistical test. The result was satisfactory (kappa = 0.71).

Table 1 presents the classification of the studies regarding the dimension of generation of the allocation sequence in the fields. In both groups, 43% of the studies presented low risk of bias (89 on oral health and 92 on ENT). No significant differences in the distribution of the studies were observed in comparing between the fields ($P > 0.943$). More than half of the RCTs in the two groups were classified as presenting uncertain risk of bias (108 on oral health and 114 on ENT) and approximately 4% in the two groups presented high risk of bias (9 on oral health and 8 on ENT).

Table 2 shows the classification of the studies with regard to allocation concealment in the fields of ENT and oral health. For this dimension, 26% of the RCTs on oral health were considered to present low risk of bias and 19% on ENT (54 on oral health and 40 on ENT). No significant differences in the distribution of the studies were observed in comparing between the two groups ($P > 0.124$). In addition, 73% of the oral health RCTs and 80% of those within ENT were classified presenting uncertain risk of bias (151 on oral health and 171 on ENT). Less than 2% in both groups presented high risk of bias (one on oral health and three on ENT).

Table 3 presents the percentages of the RCTs that were controlled for selection bias in the two groups. Lack of control over selection bias was present in 80% of the studies evaluated in the two groups. Only 38 (18%) of the studies evaluated within oral health and 28 (13%) within ENT were RCTs with control over selection bias or with low risk of selection bias. The odds ratio (OR) was 1.45, with a range from 0.85 to 2.47, which was therefore not significant. The chance that a study would be an RCT with low risk

Table 1. Classification of risk of bias in 420 studies regarding the dimension of random sequence generation in the Cochrane oral health and otorhinolaryngology (ear, nose and throat, ENT) groups

		Groups		Total	Pearson chi-square test
		Oral health	ENT		
Random sequence generation	**Low risk of bias**				0.943
	Frequency	89	92	181	
	% within allocation Sequence generation	49.20%	50.80%	100.00%	
	% within subject	43.20%	43.00%	43.10%	
	% of total	21.20%	21.90%	43.10%	
	Uncertain risk of bias				
	Frequency	108	114	222	
	% within allocation Sequence generation	48.60%	51.40%	100.00%	
	% within subject	52.40%	53.30%	52.90%	
	% of total	25.70%	27.10%	52.90%	
	High risk of bias				
	Frequency	9	8	17	
	% within allocation Sequence generation	52.90%	47.10%	100.00%	
	% within subject	4.40%	3.70%	4.00%	
	% of total	2.10%	1.90%	4.00%	
	Total				
	Frequency	206	214	420	
	% within allocation Sequence generation	49.00%	51.00%	100.00%	
	% within subject	100.00%	100.00%	100.00%	
	% of total	49.00%	51.00%	100.00%	

Table 2. Classification of risk of bias in 420 studies regarding the dimension of allocation concealment in the Cochrane oral health and otorhinolaryngology (ear, nose and throat, ENT) groups

		Groups		Total	Pearson chi-square test
		Oral health	ENT		
Allocation concealment	**Low risk of bias**				0.124
	Frequency	54	40	94	
	% within concealment allocation	57.40%	42.60%	100.00%	
	% within subject	26.20%	18.70%	22.40%	
	% of total	12.90%	9.50%	22.40%	
	Uncertain risk of bias				
	Frequency	151	171	322	
	% within concealment allocation	46.90%	53.10%	100.00%	
	% within subject	73.30%	79.90%	76.70%	
	% of total	36.00%	40.70%	76.70%	
	High risk of bias				
	Frequency	1	3	4	
	% within concealment allocation	25.00%	75.00%	100.00%	
	% within subject	0.49%	1.40%	1.00%	
	% of total	0.24%	0.70%	1.00%	
	Total				
	Frequency	206	214	420	
	% within concealment allocation	49.00%	51.00%	100.00%	
	% within subject	100.00%	100.00%	100.00%	
	% of total	49.00%	51.00%	100.00%	

of selection bias was almost 1.5 times greater in the oral healthcare group than in the ENT group.

Different methods were used for generating the allocation process. Most of the authors used unrestricted randomization to generate the allocation sequence, like computer programs or tables or lists of random numbers. Flipping a coin was used only in the oral health group. Central randomization was used only in the ENT group. Some authors used restricted randomization, like randomization in blocks: this was seen both in the ENT group and in the oral health group. Only three authors used minimization in the ENT group and only two used minimization in the oral health group. Only one author used random allocation by drawing lots, and this was within oral health (**Figure 1**).

Most of the authors used sealed numbered envelopes to accomplish allocation concealment. Only two studies used central allocation to achieve concealment in the ENT group and one study in the oral health group (**Figure 1**).

DISCUSSION

Many study projects may control for large numbers of types of bias, but the means used for adequately applying the allocation process in order to control selection bias is precisely the feature that distinguishes RCTs from other types of study project.[9]

In the present study, it was found that selection bias was possible in most of the studies evaluated in both fields. The dimension of allocation concealment appears to be a limiting factor with regard to production of RCTs with low risk of bias, thus representing the main barrier against production of RCTs with control over selection bias. Only 16% of the studies were truly RCTs or enabled control over selection bias.

The two groups were identical regarding control over selection bias and, thus, this appears not to be a condition relating only to the field of oral health. This result was unexpected, because some studies[16-17,19,23,27,30-32,34] have shown that RCTs within oral health were of poor or inadequate quality.

Similarly, Peters (2015) assessed the quality of reports and abstracts of RCTs within the literature relating to otorhinolaryngology and found that the quality of reporting of RCTs was suboptimal. This author showed that these articles did not report the allocation process sufficiently.

The only study comparing medicine with dentistry was by Sjögren,[17] yet the scale that this author used to evaluate RCTs was the Jadad quality assessment scale. Moreover, the sample was too small: only 200 in each field. The allocation implementation process, which included generation of a random allocation sequence and allocation concealment, was not simultaneous.

There is a dynamic movement towards enhancement of reports and specifically the quality of RCTs, within all fields.[16-38] Some authors have shown that improvements in the methodology of published studies within the field of oral health have been achieved. Nonetheless, great concern remains regarding description and reporting of the methods used, in published RCTs.[27,32]

There was similarity between the fields regarding the methods used in the allocation process. Simple random allocation is the easiest and most basic approach towards providing unpredictability of treatment assignment. Good methods of generating random allocation sequences include using a random-numbers table or a computer software program to generate the random sequence. There are manual methods for achieving random allocation, such as tossing a coin, drawing lots or throwing dice. However, these manual methods in practice often become nonrandom, are difficult to implement and do not leave an audit trail.[31]

To achieve allocation concealment, opaque sealed envelopes were used in both groups. This method is usually considered acceptable, but it may be susceptible to manipulation. Central randomization is the preferred method.[18]

Randomization reduces bias in clinical trials and provides a basis for ensuring the validity of data analysis using statistical testing. It usually just requires a table of random numbers. Simple randomization is adequate for large trials, while block randomization is a method for balancing equal numbers of patients in each treatment group. Stratification allows balanced distribution of one or more confounding prognostic variables among treatment groups to ensure that the groups have similar prognoses. Block randomization and stratification improve the validity of trials with smaller numbers of patients. Computer software facilitates randomization.[29] Shulz[13,15] found that none of the restricted randomization approaches that were used for generating allocation sequences, regardless of their complexity and sophistication, were better than simple unrestricted allocation for prevention of bias.

Table 3. Frequency of randomized controlled trials with control over selection bias within the fields of ear, nose and throat (ENT) diseases and oral health

Risk of selection bias	Groups			Value			Mantel-Haenszel test
	Oral health	ENT	Total	OR	95% CI		
Low risk of bias							
Count	37	28	65				
% within subject	18%	13%	16%				
% of total	9%	7%	16%				
Uncertain or high risk of bias							
Count	169	186	355				
% within subject	82%	87%	85%	1.45	0.85	2.47	0.169
% of total	40%	44%	85%				
Total							
Count	206	214	420				
% within subject	100%	100%	100%				
% of total	49%	51%	100%				

CI = confidence interval; OR = odds ratio.

In relation to sequence and allocation concealment, Shulz[13,15] showed that deciphering does occur, most commonly because the method of allocation concealment was inadequate. Even though Altman[14] showed that carrying out allocation concealment is a very simple procedure that can be incorporated into the design of any trial, the data of the present study showed that the dimension of allocation concealment is a limiting factor with regard to production of RCTs with low risk of bias. Thus, allocation concealment is the main barrier against production of RCTs with control over selection bias.

The search for the present analysis was made only in the PubMed database, and other medical databases were excluded. However, PubMed is one of the largest and most widely available databases: it is accessed through the National Institutes of Health (NIH).

CONCLUSION

Efforts need to be made to focus on the allocation implementation process, using only a single step: generation of random allocation sequences and simultaneous implementation of the sequence in such a way that the allocation is concealed. The quality of reporting within the fields of oral health and ENT is suboptimal and needs to be improved so as to match the quality already attained in other fields of healthcare. It is of great importance to take these findings into account, in order to improve the level of evidence of future randomized controlled trials within all fields of healthcare.

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Prevalence of mental disorders among elderly men: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND: Elderly men have been characterized as a group vulnerable to suicide, motivated by loneliness, loss of loved ones and feelings of uselessness to family members.

OBJECTIVES: To ascertain the prevalence of different mental disorders among elderly men who attempted suicide.

DESIGN AND SETTING: Systematic review of observational studies developed as a result of a partnership between two postgraduate schools (Lagarto and Uberlândia).

METHODS: An electronic search was performed in eight electronic databases, including "grey literature", in January 2019. Observational studies that assessed mental disorders among men older than 60 years who attempted suicide were eligible for inclusion.

RESULTS: Among the disorders evaluated, mood disorders had the highest prevalence (42.0%; 95% confidence interval, CI: 31.0-74.0%; I^2: 0.0%; P = 0.763), followed by substance use-related disorders (41.0%; 95% CI: 8.0-74.0%; I^2: 96.4; P < 0.001) and, lastly, schizophrenic disorders (5.0%; 95% CI: 0.0%-14.0%; I^2: 80.3%; P = 0.024).

CONCLUSIONS: It seems that mood disorders and substance use-related disorders are quite prevalent among elderly men with mental disorders who attempted suicide. It is important to consider the role of healthcare services in making early diagnoses of mental disorders among elderly men, in order to diminish the chances of suicide attempts among them.

SYSTEMATIC REVIEW REGISTRATION: CRD42018105981.

INTRODUCTION

The proportion of the world population corresponding to elderly people has grown extensively and it currently represents 12.3% of the total population. It has been estimated that the prevalence of this age group may reach 21.5% by 2050.[1] Countries such as France, England and Canada are already classified as elderly countries, considering that more than 14% of their populations are older than 60 years.[2] This trend is also starting to be noticed even in emerging countries like Brazil, where elderly people account for 12.5% of the population.[3] Advances in medicine, lifestyle changes, better educational conditions and better quality of life have been correlated with aging populations.[4]

Along with the growth in the elderly population, the suicide rate among the elderly has also increased over the last few years.[5,6] In 2015, suicide was the second commonest cause of death among the elderly, only behind chronic diseases.[1] In overall terms, suicide kills more than homicides and wars together.[7] European countries and Japan are the leaders in this ranking.[8]

Suicide is such a complex and multifactorial phenomenon that its occurrence cannot be attributed to any single characteristic or event.[9] Among the groups that are more vulnerable to suicide, the proportion in the elderly population is increasing the most.[10,11] The main risk factors in this age group are systemic diseases, loss of family members, impossibility of maintaining the standard of living and mental disorders,[12,13] along with genetic factors that are potentially involved.[14,15]

Among elderly men, the number of suicides can be four times higher than among women.[9] The main cause of suicide among elderly men seems to be mental disorders.[16,17] We did not identify any evidence-based synthesis of such data.

OBJECTIVE

The aim of this study was to perform a systematic review of the literature on the prevalence of mental disorders among elderly men who attempted suicide. We sought to answer the following guiding question: "what types of mental disorders are more prevalent among elderly men who attempted suicide?".

METHODS

Protocol and registration

This systematic review was conducted in accordance with the list of PRISMA-P statements (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols)[18] and the MOOSE statements (Meta-Analyses of Observational Studies in Epidemiology),[19] along with the Cochrane guidelines.[20] The protocol for this systematic review was registered in the PROSPERO database (CRD42018105981).

Study design and eligibility criteria

The systematic review was designed to answer the guiding question, through a population, variables and outcomes (PVO) strategy. In this, the population comprised elderly men with mental disorders, the variables analyzed were different types of mental disorders and the outcome was suicide attempts. Diagnoses for the health conditions presented by this population were considered in accordance with the codes of the International Classification of Diseases, 11th revision (ICD-11).

The studies that were considered eligible were observational studies on men older than 60 years who attempted suicide (ICD-11: XE97V) and who were diagnosed as presenting any of the following: mental and behavioral disorders (ICD-11: 6); organic mental disorders including symptomatic ones (ICD-11: 6E6); schizophrenia, schizotypal and delusional disorders (ICD-11: 6A2); mood disorders (ICD-11: 6A8 and 6C4G.7); unspecified mental disorders (ICD-11: 6D1); or substance use-related disorders (ICD-11: 6C4Z). No restriction regarding year, language or publication status were imposed in this search.

The exclusion criteria were as follows: 1) studies not related to the stated objective; 2) studies that did not present segmented data for men and/or elderly people; 3) studies that dealt only with suicidal thoughts or suicide attempts; 4) review studies, brief communications, editorials, letters to the editor, case reports, theses, congress abstracts, books/book chapters, textbooks and technical reports; and 5) studies with a high risk of bias (low methodological quality).

Sources of information and search strategies

The descriptors were selected from the Descriptors in Health Sciences (DeCS) and the Medical Subject Headings (MeSH). The databases used were LILACS, PubMed (including MEDLINE), SciELO, Scopus and Web of Science. OpenThesis, OATD and OpenGrey were used to partially capture the "grey literature".

The descriptors selected were: "Elderly", "Aged", "Older", "Elder", "Man", "Men", "Male", "Males", "Suicide", "Suicides", "Suicidal", "Mental disorders", "Psychiatric Illness", "Psychiatric diagnosis", "Behavior disorders", "Mood disorders", "Affective disorders" and "Personality disorders". The Boolean operators "AND" and "OR" were used to enhance the search strategy through several combinations (**Table 1**). The bibliographic search was performed in January 2019. The results obtained were exported to the Mendeley™ software (Elsevier™, Amsterdam, Netherlands), in which duplicates were removed electronically. The remaining results were exported to Microsoft Word™ 2010 (Microsoft™ Ltd, Washington, USA) and the remaining duplicates were removed manually.

Study selection

The studies were selected in three phases. In the first phase, as a calibration exercise, the reviewers discussed the eligibility criteria and applied them to a sample of 20% of the studies retrieved, in order to determine the inter-examiner agreement. After achieving a proper level of agreement (Kappa ≥ 0.81), two eligibility reviewers performed a methodical analysis on the titles of the studies, independently. The reviewers were not blind to the names of authors and journals.

In the second phase, the reviewers read the abstracts of the remaining studies, independently. Results in which the titles met the objectives of the study but for which the abstracts were not available were maintained for phase three. Lastly, the studies that had previously been considered eligible, and which were obtained and assessed, were read in full (third phase) to verify whether they met the eligibility criteria.

When the two reviewers disagreed, a third reviewer was consulted to make a final decision. The studies rejected were registered separately, with explanations for the reasons for exclusion.

Data extraction

After the studies had been selected, they were analyzed by two reviewers, who extracted data independently to gain the following information: authors, location and year of publication, time of assessment, sample characteristics (number and age group), sources of information on attempted or completed suicide, sources of demographic information, mental disorders, outcomes assessed, method for diagnosing mental disorder, prevalence of mental disorders in the group of elderly men who attempted suicide and main result of the study. In order to ensure consistency between the reviewers, a calibration exercise was performed with the two reviewers, in which they extracted the information together from an eligible study. Any disagreement between the reviewers was resolved through discussions

and when both reviewers could not agree, a third reviewer was consulted to make a final decision.

The prevalence values for each category of mental disorder, according to the ICD-11, were collected or calculated when required. When calculation of the prevalence and respective confidence interval was required, data regarding the absolute number of individuals with each type of disorder were extracted, along with the total numbers of elderly people with mental disorders and who attempted suicide.

Individual risk of bias and methodological quality assessment of the studies included

The Joanna Briggs Institute critical appraisal tools for prevalence studies were used to assess the risk of bias among the studies included.[21] Two authors performed assessments independently, in accordance with the PRISMA-P statement.[18] Any disagreement between the reviewers was resolved through discussions on the topics assessed, and when the two reviewers could not agree, a third reviewer was consulted to make a final decision.

Table 1. Search strategies in databases

Databases	Search strategy (January 2019)	Results
PubMed http://www.ncbi.nlm.nih.gov/pubmed	("Elderly"[All Fields] OR "Aged"[All Fields] OR "Older"[All Fields] OR "Elder"[All Fields]) AND ("Man"[All Fields] OR "Men"[All Fields] OR "Male"[All Fields] OR "Males"[All Fields]) AND ("Suicide"[All Fields] OR "Suicides"[All Fields] OR "Suicidal"[All Fields]) AND ("Mental Disorders"[All Fields] OR "Psychiatric Illness"[All Fields] OR "Psychiatric Diagnosis"[All Fields] OR "Behavior Disorders"[All Fields] OR "Mood Disorders"[All Fields] OR "Affective Disorders"[All Fields] OR "Personality Disorders"[All Fields])	4,941
Scopus (Elsevier) http://www.scopus.com/	("Elderly" OR "Aged" OR "Older" OR "Elder") AND ("Men" OR "Males") AND ("Suicide") AND ("Mental Disorders" OR "Psychiatric Illness" OR "Psychiatric Diagnosis" OR "Behavior Disorders" OR "Mood Disorders" OR "Affective Disorders" OR "Personality Disorders")	5,843
Web of Science (Clarivate Analytics) http://apps.webofknowledge.com/	(("Elderly" OR "Aged" OR "Older" OR "Elder") AND ("Man" OR "Men" OR "Male" OR "Males") AND ("Suicide" OR "Suicides" OR "Suicidal") AND ("Mental Disorders" OR "Psychiatric Illness" OR "Psychiatric Diagnosis" OR "Behavior Disorders" OR "Mood Disorders" OR "Affective Disorders" OR "Personality Disorders"))	390
LILACS (Virtual Health Library) http://lilacs.bvsalud.org/	("Elderly" OR "Aged") AND ("Man" OR "Male") AND ("Suicide") AND ("Mental Disorders") AND (instance:"regional") AND (db:("LILACS"))	52
	tw:(("Older" OR "Elder") AND ("Men" OR "Males") AND ("Suicide") AND ("Mental Disorders")) AND (instance:"regional") AND (db:("LILACS"))	3
	tw:(("Elderly" OR "Aged") AND ("Man" OR "Male") AND ("Suicide") AND ("Psychiatric Illness ")) AND (instance:"regional") AND (db:("LILACS"))	1
	tw:(("Elderly" OR "Aged") AND ("Man" OR "Male") AND ("Suicide") AND ("Psychiatric Diagnosis")) AND (instance:"regional") AND (db:("LILACS"))	31
	tw:(("Elderly" OR "Aged") AND ("Man" OR "Male") AND ("Suicide") AND ("Behavior Disorders")) AND (instance:"regional") AND (db:("LILACS"))	31
	tw:(("Elderly" OR "Aged") AND ("Man" OR "Male") AND ("Suicide") AND ("Mood Disorders")) AND (instance:"regional") AND (db:("LILACS"))	9
SciELO http://www.scielo.org/	"Suicide" AND "Mental Disorders" AND "Elderly"	5
	"Suicide" AND "Mental Disorders" AND "Older"	7
	"Suicide" AND "Mental Disorders" AND "Aged"	11
	"Suicide" AND "Psychiatric Illness" AND "Aged"	0
	"Suicide" AND "Mood Disorders" AND "Aged"	7
	"Suicide" AND "Behavior Disorders" AND "Aged"	0
OpenThesis http://www.openthesis.org/	("Aged" OR "Older" OR "Elder") AND ("Male") AND ("Suicide") AND ("Mental Disorders" OR "Psychiatric Illness" OR "Psychiatric Diagnosis" OR "Behavior Disorders" OR "Mood Disorders" OR "Affective Disorders" OR "Personality Disorders")	1,560
OATD https://oatd.org/	("Aged" OR "Older" OR "Elder") AND ("Male") AND ("Suicide") AND ("Mental Disorders" OR "Psychiatric Illness" OR "Psychiatric Diagnosis" OR "Behavior Disorders" OR "Mood Disorders" OR "Affective Disorders" OR "Personality Disorders")	3
OpenGrey http://www.opengrey.eu/	("Aged") AND ("Male") AND ("Suicide") AND ("Mental Disorders")	0
PsycNet (American Psychological Association) https://psycnet.apa.org/search/basic	(("Elderly" OR "Aged" OR "Older" OR "Elder") AND ("Man" OR "Men" OR "Male" OR "Males") AND ("Suicide" OR "Suicides" OR "Suicidal") AND ("Mental Disorders" OR "Psychiatric Illness" OR "Psychiatric Diagnosis" OR "Behavior Disorders" OR "Mood Disorders" OR "Affective Disorders" OR "Personality Disorders"))	**877**
Total		**13,771**

The questions assessed were the following: Q1) Was the sample frame appropriate for addressing the target population? Q2) Were the study participants sampled appropriately? Q3) Was the sample size adequate? Q4) Were the study subjects and the setting described in detail? Q5) Were the data analyzed with sufficient coverage of the sample identified? Q6) Were valid methods used for identifying the condition? Q7) Was the condition measured in a standard and reliable way for all participants? Q8) Was the statistical analysis adequate? Q9) Was the response rate adequate, and if not, was the low response rate managed appropriately?

Each study was categorized according to the percentage of positive answers in the questions corresponding to the assessment tool. Risk of bias was considered high when up to 49% of the answers were "yes", moderate when 50% to 69% of the answers were "yes" and low when than 70% of the answers were "yes".[21]

Synthesis of results and meta-analysis

A synthesis was performed on the results, with descriptive meta-analysis on the studies included, and this was presented narratively and through tables and figures. The prevalence estimated for each mental disorder considered was calculated using fixed and random-effect models in the meta-analysis, as indicated. The choice of proper effect for correctly representing the results was based on the heterogeneity presented. When heterogeneity was high ($I^2 > 50\%$ or chi-square P-value < 0.05), the random-effects model was selected.[22]

Quality of evidence-gathering

Quality of evidence and recommendation strength were assessed using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) tool.[23] The GRADE pro-GDT software (http://gdt.guidelinedevelopment.org) was used for summarizing the results. This assessment was based on study design, methodological limitations, inconsistencies, indirect evidence, imprecision and other considerations. The quality of evidence was characterized as high, moderate, low or very low.[23]

RESULTS

Study selection

During the first phase of study selection, 12,894 results were found, distributed in eight electronic databases, including the grey literature. After removing duplicate results, 9,032 studies were retained for analysis of titles and abstracts. After this, 18 eligible results were retained for full-text analysis. After reading the full text, 16 of these studies were eliminated because they did not deal only with suicidal ideation or completed suicide and did not present segmented data for men and/or elderly people. Lastly, a database specific to mental health was researched (PsycNet, from the American Psychological Association). Through following the same analysis stages as used in relation to other databases, 877 results were initially identified, but none of them met the inclusion criteria. Thus, in the end, only two studies were selected for qualitative analysis and meta-analysis. The flow diagram shown in **Figure 1** describes the process of searching for, identification, inclusion and exclusion of articles.

Characteristics of eligible studies

The studies were published between 2004 and 2016 and were conducted in Finland[24] and Australia.[25] Regarding study design, Almeida et al.[25] undertook a cohort study while Suominen et al.[24] did a cross-sectional study. Both studies[24,25] reported that ethical approval had been obtained for accessing the diagnostic data and patient characterization data. Almeida et al.[25] collected data from the Western Australian Data Linkage System (WADLS), based on community-dwelling information, while Suominen et al.[24] used data obtained from four general hospitals based on records from patients who had been treated for suicide attempts. Although neither of these could be considered to be a balanced epidemiological study, both seem to somehow represent an extended population range. One of the articles[24] was part of a multicenter study (WHO/EURO Multicentre Study on Parasuicide). However, the definition of elderly participants differed between these two studies: one[24] defined the age group as over 60 years while the other[25] defined it as 65 years. For statistical analyses, while Suominen et al.[24] divided the population studied into two groups (< 60 years and ≥ 60 years), Almeida et al.[25] considered four groups (65-69 years, 70-74 years, 75-79 years and ≥ 80 years). Additional details are presented in **Table 2**.

Risk of individual bias of the studies

One of the studies[24] presented moderate risk of bias (66.6%), while the other[25] presented low risk of bias (77.7%). The study by Suominen et al.[24] did not present adequate sample size (Q3), data analysis (Q5) or response rate (Q9). The study by Almeida et al.[25] did not present adequate data analysis (Q5) or response rate (Q9).

Synthesis of results and meta-analysis

These two studies presented different results after their statistical analyses had been performed, but it has to be borne in mind that they did not have the same objective. Suominen et al.[24] observed that there was no statistically significant difference in the number of suicide attempts between the sexes. They also found that only one-fifth of the elderly individuals who attempted suicide were older than 75 years and that most of the elderly subjects had contacted primary healthcare before the attempt. Only 38% of the elderly subjects who attempted suicide for the first time had been diagnosed with mood disorders before the suicide attempt.

Among those who made a second suicide attempt, 61% had previously undergone psychiatric treatment.

Almeida et al.[25] observed that the main variable associated with suicide attempts among the elderly was the existence of previous attempts (hazard ratio, HR 203.14; 95% confidence interval, 95% CI 164.10-251.46). When the data of participants with a history of attempted suicide were removed from the multivariate analysis, bipolar disorder took over as the main associated variable (HR 15.46; 95% CI 9.71-24.62). The elderly men who committed suicide were 3.6 years younger than the elderly men who did not did not die when they attempted suicide.

In the two studies included, a total of 359 elderly people with mental disorders who had attempted suicide were identified. Only three types of mental disorders were reported in both studies and consequently could be synthetized into a single measurement of overall prevalence. Thus, the prevalences of mood disorders (ICD-11: 6A8 and 6CAG.7), schizophrenic disorders (ICD-11: 6A2) and substance use-related disorders (ICD-11: 6C4Z) were ascertained.

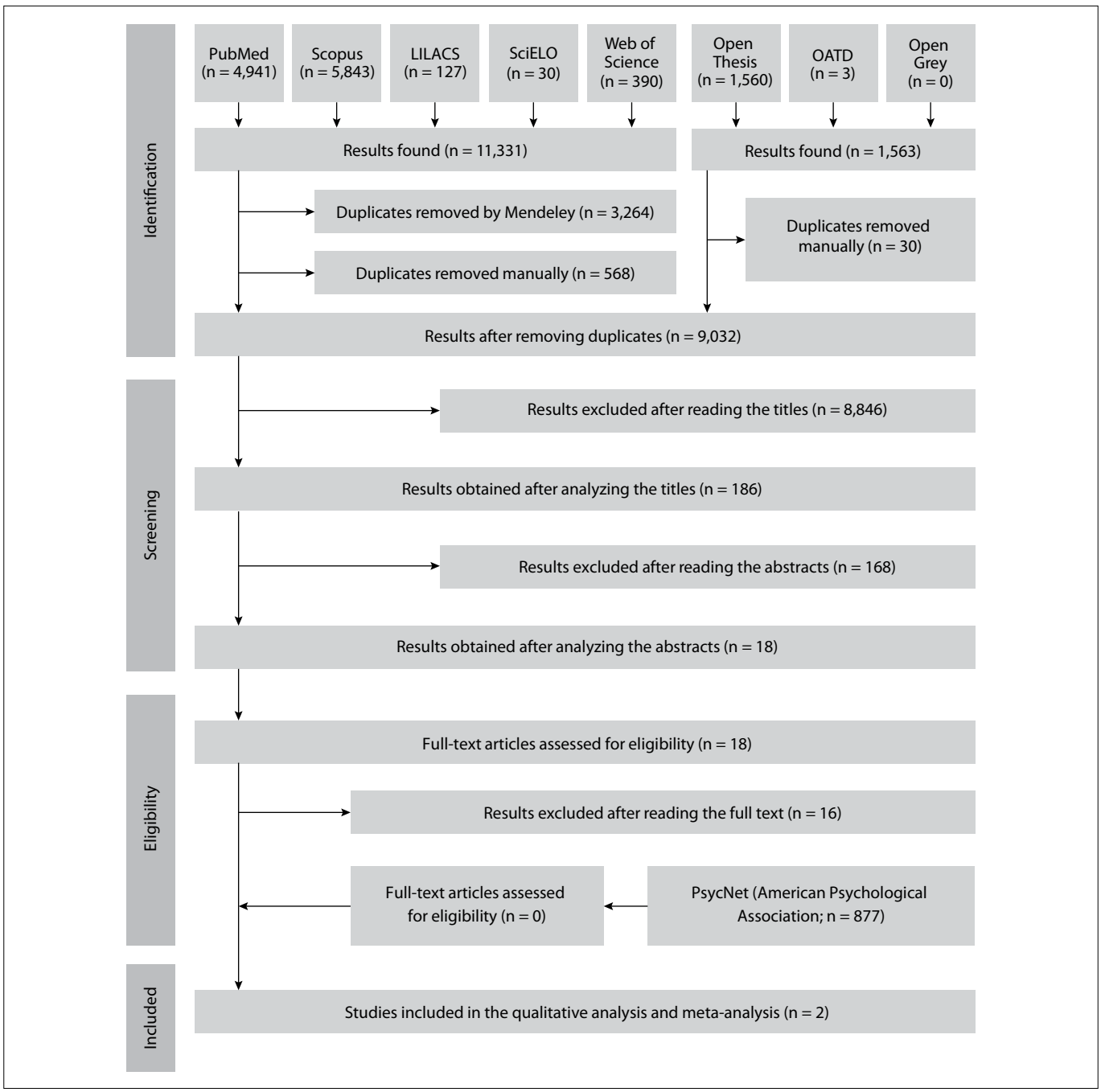

Figure 1. PRISMA flow diagram.

The mental disorders observed by Suominen et al.[24] were personality disorders (3.64%), mood disorders (43.64%), schizophrenic disorders (10.91%), substance use-related disorders (23.64%), neurotic disorders (9.09%) and other mental disorders (9.09%). The results from their study suggested that mood disorders remained undiagnosed within primary healthcare before the suicide attempt.

The mental disorders observed by Almeida et al.[25] were bipolar disorders (33.57%; 95% CI 23.59-47.79), depression (21.85%; 95% CI 16.61-28.74), schizophrenic disorders (4.71%; 95% CI 1.73-12.84), alcohol-related disorders (12.21%; 95% CI 9.28-16.07) and disorders relating to other substances (3.49%; 95% CI 2.69-4.52). They concluded that previous suicide attempts were associated with new suicide attempt episodes, but not with completion of the act, while psychological disorders were associated with deaths by suicide.

The pooled prevalence of the mental disorders assessed ranged from 5.0% to 42.0% and the highest prevalence occurred in cases of mood disorders (42.0%; 95% CI 31.0-74.0%; I^2 0.0%; P = 0.763), followed by substance use-related disorders (41.0%; 95% CI 8.0-74.0%; I^2 96.4; P < 0.001). These estimates were obtained using a fixed-effects model and a random-effects model, respectively. **Figure 2a** (mood disorders) and **Figure 2b** (substance use-related disorders) show the measurements for these two disorders. Schizophrenic disorders were the least prevalent (5.0%; 95% CI 0.0-14.0%; I^2 80.3%; P = 0.024), as shown in **Figure 2c**.

In addition to the outcomes assessed in the meta-analyses, other mental disorders were identified, but it was not possible to estimate their overall prevalence, given that data on these other conditions were only presented in a single study.[25]

Certainty of the evidence identified

The certainty of the evidence identified was divided into levels that were assessed using the GRADE tool.[23] The certainty level for the outcome relating to the prevalence of mood disorders was classified as low, which means that the true effect may have been substantially different from the estimated effect. Moreover, the certainty level for outcomes relating to substance use-related disorders and schizophrenic disorders was classified as very low, which means that the true effect was probably substantially different from the estimated effect (**Table 3**). The design of the study was responsible for downgrading by two levels in relation to all outcomes. Moreover, the high inconsistency gave rise to downgrading by two levels in relation to two outcomes (substance use-related disorders and schizophrenic disorders).

DISCUSSION

Although this systematic review suggested that there was higher prevalence of some types of mood disorders among the elderly people who attempted suicide, the level of certainty for support this statement was limited. It had previously been reported that elderly men presented higher vulnerability towards committing suicide.[24,26-29] This behavior is usually explained in terms of diagnoses of chronic diseases that interfere with quality of life,[30,31] or in terms of loneliness, loss of a family member or even boredom or lack of employment.[32]

It is important to consider whether these factors may trigger depression, which would strengthen the results from our systematic review, considering that depression presented significant prevalence among the mental diseases considered in the eligible articles. In this regard, an increasing curve of diagnoses of depression has been observed among elderly people over the last decade, caused mainly by loneliness or feelings of uselessness to society.[33,34] Studies conducted in different countries and with different age groups have strongly correlated depression with suicidal tendencies[28,35] and have shown that there is a relationship between depression and suicide among elderly men.[25,36] Corroborating this information, it has been observed that 70%

Table 2. Summary of the main characteristics of the eligible studies

Author	Study location	Assessment time	Total sample	Age group	Sources of information	Diagnostic method for mental disorder	Mental disorders assessed	Outcomes assessed
Suominen et al.[24]	Helsinki, Finland	1 year (1997-1998)	81	≥ 60	Medical records from four general hospitals in Helsinki	ICD-10	Schizophrenic disorders Mood disorders Substance use-related disorders Neurotic disorders Personality disorders Other mental disorders	Suicide rate within 12 months after hospital release
Almeida et al.[25]	Perth, Australia	16 years (1996-2011)	38,170	> 65	Western Australian Data Linkage System (WADLS)	ICD-8 ICD-9 ICD-10	Depression Bipolar disorder Psychoses Dementia Alcohol-related disorders Substance use-related disorders	Rates of suicide and suicide attempts

ICD = International Classification of Diseases.

of elderly people older than 70 years who committed suicide also presented depression.[37]

Another mood disorder that has previously been studied is bipolar disorder. Almeida et al.[25] showed that elderly people with bipolar disorder were 33 times more likely to commit suicide after the first attempt. These authors[25] also suggested that, among mental disorders, bipolar disorder increases the likelihood of a second suicide attempt. A correlation between bipolar disorder and suicide has been observed in all age groups, along with a tendency among people with type II bipolar disorder to use more violent and lethal methods in their suicide attempts, compared with individuals with type I.[38] Suicide among people with bipolar disorder has been found to be influenced by seasonal factors.[39] Drug treatment is essential to prevent suicide in this population, and use of a combination of mood stabilizers and antidepressants has been correlated with lower risk of suicide.[40]

Schizophrenic disorders were also correlated with higher numbers of suicide attempts in the studies that were considered eligible for the present analysis. Schizophrenic disorders presented the lowest prevalence among the elderly men with mental disorders in this systematic review. These data are concordant with findings in other studies of reduction of diagnostic volume

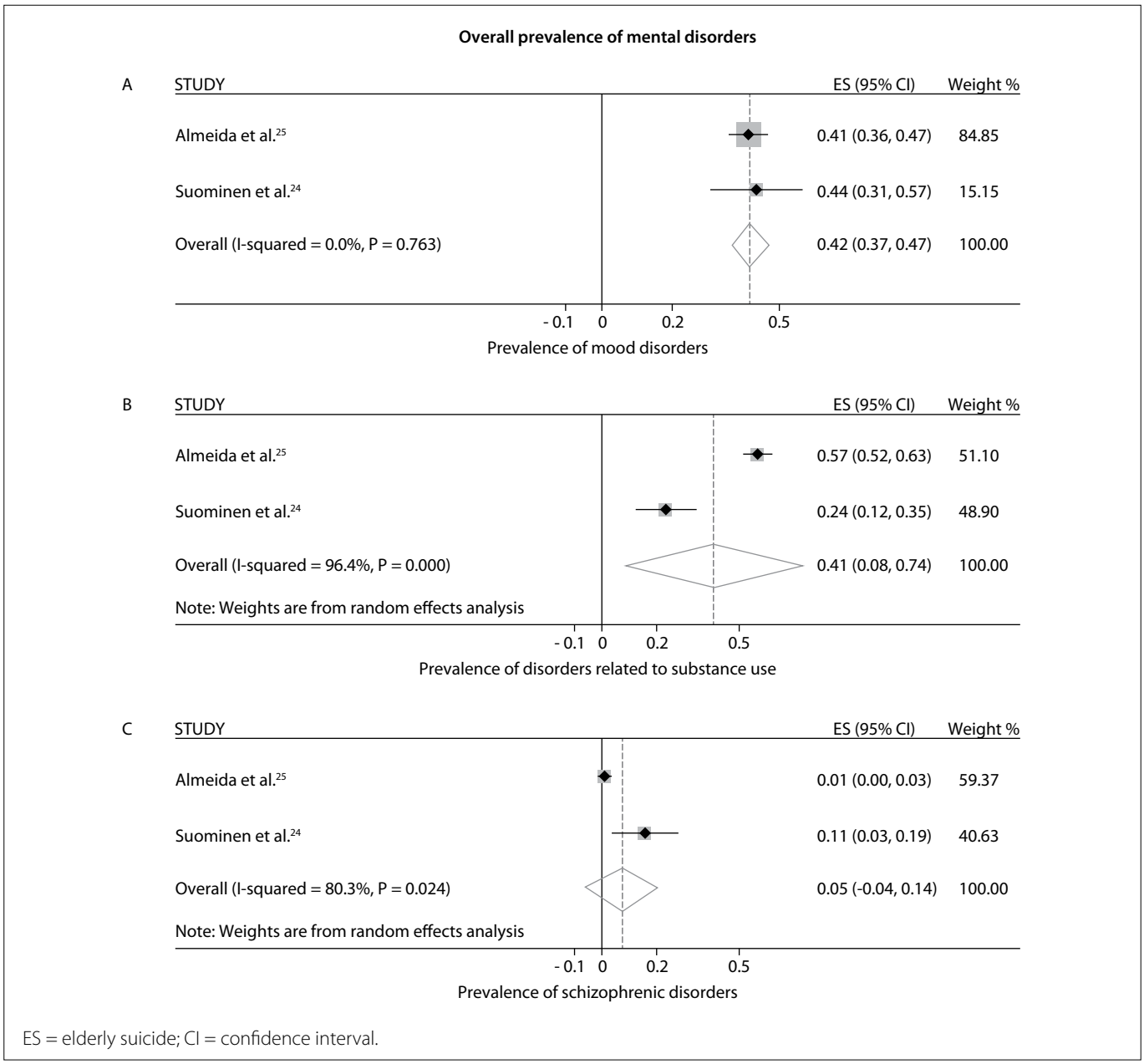

Figure 2. Overall prevalence of each type of mental disorder according to the meta-analyses using fixed and random effects: (a) mood disorders; (b) substance use-related disorders; and (c) schizophrenic disorders.

of this type of mental disorder that was observed as age progressed among elderly men.[37] Elderly men with schizophrenia were found to be 4.71 times more likely to commit suicide[25] and the number of attempts in this population was strongly correlated with the number of suicides actually committed.[41] Use of alcohol has also been found to be a strong predictor among schizophrenics indicating that they may commit suicide.[41] Hor and Taylor[41] affirmed that the best suicide prevention strategy for schizophrenic patients should be to stimulate them to adhere better to drug therapy. These findings emphasize the importance of timely diagnosis and adequate treatment of mental disorders among elderly men.

It is known that suicide is more prevalent among men.[9,16,17,19,42-45] It affects elderly people at higher rates,[5,7,8,10,11,13] and elderly men use more violent methods of suicide, with emphasis on hanging.[37] Suicide attempts are therefore a major marker for identifying suicidal behavior, and need to be considered in treatment planning and suicide prevention.[46] Hence, through presenting the prevalence of suicide attempts for each disorder analyzed, the information collected in our systematic review may be helpful in planning improved care for elderly men and it emphasizes the importance of timely adequate diagnosis for these mental disorders.[38,39,47]

Mainly regarding mood disorders, which were more predominantly correlated with suicide attempts in the present meta-analysis, the importance of primary healthcare in determining an early diagnosis needs to be strengthened. If such disorders fail to be satisfactorily diagnosed before the suicide attempt,[24] this may constitute a significant factor relating to the attempt. Among mental disorders, implementation of the correct drug therapy seems to stand out as the best way to prevent suicide.[40,41]

Moreover, the number of suicide attempts might be even higher than the estimated number. This underestimation may arise through potential failures in reporting or undervaluation of suicide outcomes because of other diagnoses. Hence, it is important to consider the role of healthcare services in making early diagnoses of mental disorders among elderly men, in order to propose timely and adequate treatment. In cases of attempted suicide, higher levels of care for these patients should be provided, considering that a new attempt may occur or suicide may even be completed.

Quality of evidence

Using the GRADE tool, the overall quality of evidence was identified as low or very low, depending on the outcomes assessed. This was corroborated by the observational designs of the studies analyzed here, given that such designs generally only attain lower scores when the GRADE assessment tool is used. Moreover, the inconsistency in the prevalence of mental disorders among the studies included downgraded the level of evidence. Lastly, in addition to the potential for underreporting that is usually associated with secondary data on suicide, the quality of evidence is also adversely affected by contextual issues (esteem and pressure in the legal, religious and political environments); diagnostic difficulties in some cases (self-starvation, falls, drowning, car accidents, opiate overdose and euthanasia); and the lack of an internationally standardized procedure for reporting suicide.

Table 3. Summary of findings according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for the outcomes of the systematic review and meta-analysis

Quality assessment						Summary of results			Significance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effects	General quality	
Outcome I: Prevalence of mood disorders									
2	Observational	Not severe	Not severe	Not severe	Not severe	None	Fixed (95% CI) 42% (31.0-74.0%)	⊕⊕ Low	Critical
Outcome II: Prevalence of substance use-related disorders									
2	Observational	Not severe	Very severe[1]	Not severe	Not severe	None	Random (95% CI) 41% (8.0-74.0%)	⊕ Very low	Critical
Outcome III: Prevalence of schizophrenic disorders									
2	Observational	Not severe	Very severe[1]	Not severe	Not severe	None	Random (95% CI) 5% (0.0-14.0%)	⊕ Very low	Critical

GRADE Working Group grades of evidence

High certainty: Very confident that the true effect is close to the estimated effect.

Moderate certainty: Moderately confident in the effect estimated. The true effect is likely close to the estimated effect, but it may be substantially different.

Low certainty: Limited confidence in the effect estimated. The true effect may be substantially different from the estimated effect.

Very low certainty: Very little confidence in the effect estimated. The true effect is likely substantially different from the estimated effect.

[1]Downgraded by two levels because of high heterogeneity ($I^2 > 50\%$).

CI = confidence interval.

Limitations

Suicide is an important public health problem that affects both developed and developing countries.[1] In this review, the studies on suicide attempts among elderly men with mental disorders that were included were only conducted in developed countries. Thus, the main limitation of the present study is the low level of certainty of its evidence. Another limitation is the lack of research from countries with emerging economies, which prevents generalization of the data obtained to a global reality. Moreover, the high methodological heterogeneity and the low number of eligible studies suggest that there is a need to conduct further studies with improved designs, to obtain stronger scientific evidence that would lead to more conclusive findings regarding this important topic.

CONCLUSION

It seems that mood disorders and substance use-related disorders are quite prevalent among elderly men with mental disorders who attempt suicide. Significant imprecision (large prevalence ranges) was associated with low certainty of evidence. Hence, the mean prevalence summaries provided here should be carefully considered, given that real population values may differ substantially from the stated synthetized prevalence. Nevertheless, it seems important to consider the role of healthcare services in making early diagnoses of mental disorders among elderly men, with the aim of diminishing the chances of suicide attempts among them. Since suicide is a multifactorial affliction, the focus should not only be on mental disorders but also be on all factors associated with suicide.

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ORIGINAL ARTICLE

Impact of physical activity during weekdays and weekends on fat mass among adults: 12-month cohort study

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ABSTRACT

BACKGROUND: Physical activity (PA) practices seem to differ between weekdays and weekends and these pattern changes can affect body fat differently. However, previous studies did not assess the mediation effect of weekday and weekend PA on maintenance of body fat using sophisticated statistical models.

OBJECTIVE: To analyze the mediation effect of PA during weekdays and weekends on maintenance of fat mass over a 12-month follow-up.

DESIGN AND SETTING: Longitudinal cohort study (12 months) conducted at a public university in Presidente Prudente, Brazil.

METHODS: A sample of 225 adults (117 females) was used. Body fatness and fat mass were assessed using dual-energy X-ray absorptiometry. PA levels were assessed using a pedometer. The statistical analysis consisted of paired-sample t tests, independent-sample t tests, Pearson correlations and mediation models.

RESULTS: After 12 months, weekend PA had decreased while body composition indicators remained stable (without changes). The correlation between fat mass at baseline and follow-up was high for both sexes (men: 0.966; women: 0.941; P-value = 0.001 for both). Moreover, PA indices were inversely but moderately related to fat mass at baseline and follow-up. Lastly, weekend PA mediated the association between fat mass at baseline and follow-up (P-value < 0.05) by around 2% and 4%.

CONCLUSION: Weekend PA mediated the association between fat mass at baseline and fat mass after one year of follow-up among these adults. Further studies are required to investigate the association between physical activity, body fat and other variables such as dietary patterns and sleep time.

INTRODUCTION

Independently of age, accumulation of fat mass has adverse effects on human health, mainly because obesity is involved in the genesis of chronic diseases,[1] and it increases the risk of mortality.[2] The harmful effects of adiposity on health are well known, but even so, the prevalence of overweight and obesity is still high around the world.[3] Consequently, medicines, diets and physical activity have been used to change this scenario and its statistics.[4]

Regarding physical activity, studies have shown an independent inverse association between physical activity and body fatness.[5] Moreover, different intensities and patterns of physical activity seem to present distinct dose-response relationships with body fat, given that activities with higher intensities, such as physical exercise, have a more significant effect on adipose tissue.[6]

However, habitual physical activity among adults constitutes a complex form of human behavior that is strongly affected by social factors. Physical activity guidelines for adults usually adopt recommendations based on five days per week (150 minutes/week, i.e. five days with 30 minutes of activity),[7] in allusion to the number of working days.

In this kind of approach, the role of physical activity performed during the weekend is underestimated, probably because in our society Saturdays and Sundays are usually a time to restore the energy spent during the regular week. In fact, the weekend could be the perfect moment to engage in moderate-to-vigorous leisure-time physical activity/exercise because it is less influenced by activities that consume time (e.g., job, traffic or children's schooling). However, it is unclear whether physical activities performed over the weekend have any effect on the health status of adults.[8]

The evidence regarding possible "weekend warrior" effects (a term that was created to characterize individuals who gather much of their physical activity especially through physical exercise

on weekends, thus creating irregular patterns of physical activity[8,9]) is divergent. It has been shown that a session of physical activity during the weekend can be a protective factor against cardiovascular risk,[10] but on the other hand, the risk of injuries increases.[8] From the perspective of free-living physical activity, it is also not clear what the effect of weekend physical activity on body composition is. Drenowatz et al.[11] found that an increase in physical activity levels during weekends over a one-year follow-up was associated with a decrease in fat mass.

However, previous studies did not assess the effect of physical activity during weekdays and weekends on maintenance of body fat using sophisticated statistical models. Multivariate models like linear regression (which were usually adopted in previous studies) identify simultaneous relationships among different variables (direct causal relationships) but do not capture some relevant components of these relationships, such as mediation effects. Mediation analysis enables a more robust understanding of the causal influence of the mediator in the relationship between the exposure and the outcome. Based on previous findings, our hypothesis was that physical activity during weekends could be a protective factor against body fat.[8,12]

OBJECTIVE

The aim of this study was to analyze the mediation effect of physical activity during weekdays and weekends on maintenance of fat mass among adults, over one year of follow-up. The initial hypothesis was that physical activity during weekends would be inversely related to fat mass in adults of both sexes.

METHODS

Sample

This longitudinal study was developed in the city of Presidente Prudente, which is a medium-sized city of around 200,000 inhabitants that is located in the western region of the state of São Paulo, Brazil. This study combined data from two different cohort studies that were conducted between 2013 and 2015. The research protocols were approved by the local research ethics committee (protocol 173.571/2012 on December 14, 2012; and protocol 349.306/2013 on August 5, 2013), and all subjects signed a consent form. All the evaluations described below were performed at our university's Laboratory of InVestigation on Exercise (LIVE), and two doctoral students performed the measurements.

The researchers contacted potential participants at the university and at gyms and fitness clubs. The inclusion criteria were that participants should be aged between 30 and 60 years, without any diagnosis of previous cardiovascular complications (e.g. stroke or heart attack), without diabetes complications (amputation or visual problems) and without limitations on physical activity. The sample comprised university staff (professors, administrative staff and gardening/cleaning staff) and members of gyms or fitness centers located in different geographical regions of the city.

Initially, in the two cohorts together, data-gathering was started among 320 adults, but after accounting for dropouts during the 12 months of follow-up and for missing data (incomplete data on physical activity on any of the seven days), the final sample of this study consisted of 225 participants (n = 107 from the first cohort and n = 118 from the second cohort). Data from the first cohort were collected between 2013 (baseline; n = 122) and 2014 (follow-up; n = 107) and data from the second cohort were collected between 2014 (baseline; n = 198) and 2015 (follow-up; n = 118) using similar inclusion criteria for the two cohorts. Lastly, all procedures (data collection of all variables included in the study) were performed at the first evaluation (baseline) and were repeated 12 months afterwards (follow-up).

Interview and measurements

The participants attended a face-to-face interview at which they were asked to provide personal data (general information regarding age, sex and ethnicity). On this occasion, anthropometric variables were also measured, using a digital scale for body mass (Filizola, PL-200, to the nearest 0.1 kg) and a fixed stadiometer for height (Sanny, Standard ES2030, to the nearest 0.1 cm). Lastly, from the body mass and height values, the body mass index (BMI; kg/m^2) was calculated. All these procedures were performed at the first evaluation (baseline) and again 12 months afterwards (follow-up).

Body composition

Dual-energy X-ray absorptiometry (DXA) (Lunar, DPX-MD model, USA) was used to assess body fatness (percentage values, %) and fat mass (kg). Absolute changes (Δ) and relative changes (Δ%) were calculated for body fatness and fat mass. The DXA scans and definition of lines (regions of interest, ROIs) in the body segments were performed as requested for General Electric Healthcare using a standardized protocol that had been applied in previous studies.[13,14] Before the first examination of each day, a trained researcher performed a quality control test. During the scan, the participants remained in the supine position, wearing only light clothing (without shoes). Lastly, the coefficient of variation for this device was determined as 0.66%, through whole-body bone mineral density analysis on 30 individuals who were not involved in this study.

Physical activity

At the baseline and follow-up, the amount of physical activity (described as steps) was estimated using pedometers (Yamax Digiwalker, SW200 model, Japan). There were no

recommendations from researchers regarding physical activity or diet (thus avoiding any kind of interference), but only about the use of pedometers. In accordance with those recommendations, the participants wore the pedometer fixed to one hip for seven consecutive days. The device was taken off only during periods of sleep and during any water-based activities. The participant reported the total number of steps that had been recorded by the device, at the end of every single day of the entire week. Physical activity was divided into activity on weekdays (Monday, Tuesday, Wednesday, Thursday and Friday) and activity on weekends (Saturday and Sunday). The amount of physical activity required for the participant to be classified as "active" was ≥ 7,500 steps on at least five days per week, based on the descriptions of the study by Tudor-Locke et al.[15] Taking into account both the baseline and the 12-month follow-up, absolute changes (Δ) and the sum of the baseline and follow-up were calculated for physical activity (expressed as numbers of steps).

Statistical analyses

The descriptive statistics comprised mean values and standard deviations (SD). Comparisons between the two times (baseline and follow-up) were made using a paired-sample t test. Comparisons of changes between men and women at the baseline and follow-up were made using an independent-sample t test. Pearson correlation was used to access correlations between body composition variables and physical activity during weekends and weekdays.

Mediation models were performed in accordance with previous recommendations.[12] Causal mediation was assessed such that it included exposure-mediator interactions, and the total effect was then decomposed into the controlled direct effect and the natural indirect effect, using linear regression models (paramed command).[12] The analyses were adjusted for sex, chronological age and race. After this, sensitivity analyses were conducted with the aim of estimating potential unmeasured or uncontrolled confounding factors (E-values).[16] The theoretical model is presented in **Figure 1**.

All analyses were performed using the STATA software (version 15.1). The significance level (P-value) was set at < 0.05.

RESULTS

The general characteristics of the sample are described in **Table 1** and **Table 2**. Overall, physical activity during weekends (the number of steps) decreased after one year of follow-up, for both sexes, while body composition indicators remained stable. In addition, at the baseline of the study, 73 participants (32.4%) met the 7,500-step recommendations on at least five days per week, while 152 did not reach the sufficient number of steps (**Table 2**). Comparison of the changes in physical activity and body composition between the sexes (**Table 3**) showed that only the sum of physical activity (baseline plus follow-up) was different between men and women (P-value = 0.011).

Pearson correlations are presented in **Table 4**. The correlation between fat mass at baseline and follow up was high for both sexes (men: 0.966; women: 0.941; P-value = 0.001 for both). The correlation between physical activity during weekdays and weekends was also significant. Moreover, the physical activity indices were inversely but moderately correlated with fat mass at baseline

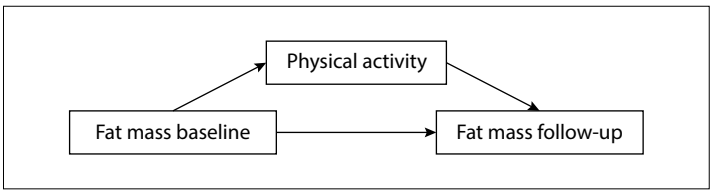

Figure 1. Theoretical model.

Table 1. Descriptive characteristics of the sample at baseline, according to sex (n = 225)

Variables	Males (n = 108)	Females (n = 117)	P-value
	Mean (SD)	Mean (SD)	
Chorological age (years)	44.34 ± 8.91	47.87 ± 9.11	0.004
Body mass (kg)	84.18 ± 13.76	69.11 ± 13.15	< 0.001
Height (cm)	175.9 ± 7.6	161.3 ± 8.0	< 0.001
Body mass index	27.20 ± 3.92	26.66 ± 5.32	0.382
Waist circumference (cm)*	92.21 ± 10.91	82.23 ± 12.75	< 0.001
Lean soft tissue (kg)	55.99 ± 7.58	37.62 ± 5.27	< 0.001

SD = standard deviation; *n = 215.

Table 2. Comparison over time between baseline and follow-up (12 months) regarding body composition variables and percentage of steps during weekends (n = 225)

Variables	Baseline	Follow-up	P-value
	Mean (SD)	Mean (SD)	
Males (n = 108)			
Adiposity			
Body fatness (%)	28.38 ± 8.37	28.11 ± 8.45	0.237
Fat mass (kg)	24.14 ± 9.74	24.08 ± 9.85	0.809
Lean soft tissue (kg)	55.99 ± 7.58	56.20 ± 7.80	0.126
Weekday physical activity			
Number of steps (n)	41,892 ± 20,799	37,110 ± 18,620	0.004
Weekend physical activity			
Number of steps (n)	14,492 ± 8,542	12,152 ± 6,704	0.008
Females (n = 117)			
Adiposity			
Body fatness (%)	40.00 ± 9.36	39.76 ± 9.16	0.503
Fat mass (kg)	27.79 ± 11.00	28.13 ± 11.28	0.337
Lean soft tissue (kg)	37.62 ± 5.27	37.81 ± 5.02	0.338
Weekday physical activity			
Number of steps (n)	38,427 ± 20,783	34,830 ± 20,644	0.006
Weekend physical activity			
Number of steps (n)	11,787 ± 6,712	10,361 ± 6,150	0.005

SD = standard deviation.

and follow up, given that the sum of physical activity (on weekends) had the greatest correlation with fat mass, for both sexes: at the baseline (men: -0.381; women: -0.307) and at the follow-up (men: -0.420; women: -0.364).

Table 3. Comparisons of changes (considering 12-month follow-up) regarding body composition and physical activity among men and women (n = 225)

Variables	Male (n = 108) Mean (95% CI)	Female (n = 117) Mean (95% CI)	P-value
Adiposity			
Absolute change (Δ)			
Body fatness (%)	-0.270 (-0.720 to 0.180)	-0.241 (-0.951 to 0.469)	0.946
Fat mass (kg)	-0.059 (-0.547 to 0.427)	0.340 (-0.359 to 1.040)	0.361
Relative change (Δ%)			
Body fatness (%)	-0.762 (-2.604 to 1.079)	0.280 (-2.334 to 2.895)	0.525
Fat mass (kg)	0.119 (-2.151 to 2.391)	2.328 (-0.988 to 5.644)	0.285
Weekday physical activity (steps)			
Sum (baseline plus follow-up)	79,003 (72,045 to 85,960)	73,258 (66,409 to 80,107)	0.192
Absolute change (Δ)	-4,782 (-7,665 to 1,900)	-3,597 (-6,858 to -337)	0.850
Weekend physical activity (steps)			
Sum (baseline plus follow-up)	26,645 (24,135 to 29,154)	22,148 (20,065 to 24,232)	0.011
Absolute change (Δ)	-2,340 (-3,851 to -828)	-1,425 (-2,528 to -322)	0.673

CI = confidence interval.

Models of the mediation by physical activity indicators on the association between fat mass at baseline and fat mass at follow-up are presented in **Table 5**. Physical activity during weekends (baseline, follow-up and the sum of baseline and follow-up) mediated the association between fat mass at baseline and follow-up (P-value < 0.05); the percentage of mediation was between 2% and 4%, and the potential influence of unmeasured confounders (E-values) ranged from 1.13 to 1.17. On the other hand, physical activity during weekdays did not mediate the association between fat mass at baseline and follow-up.

DISCUSSION

In the present study, the aim was to investigate the effect of physical activity during weekends and weekdays on maintenance of fat mass among adults, over a one-year follow-up. The main result found was that physical activity during weekends, but not weekdays, partially mediated the association between fat mass at baseline and fat mass after one year of follow-up, given that a higher amount of physical activity was associated with reduction in fat mass.

Obesity during adulthood presents high stability, even in long-term follow-up studies.[17] This may be due to the biology of fat cells, which have a characteristic of stability over several hyperplasia events.[18] In this regard, understanding the real impact of each factor on adiposity during adulthood is important, in order to support formulation of possible intervention programs. With this in mind, several factors can change the trajectory of body fatness during adulthood, especially behavioral factors, such as dietary

Table 4. Correlation between exposures, mediators and outcomes (n = 225)

	1	2	3	4	5	6	7	8
Males (n = 108)								
1. Fat mass baseline	1							
2. Fat mass follow-up	0.966**	1						
3. Physical activity baseline (weekends)	-0.339**	-0.369**	1					
4. Physical activity follow-up (weekends)	-0.316*	-0.354**	0.481**	1				
5. Physical activity sum (baseline plus follow-up) (weekends)	-0.381**	-0.420**	0.895**	0.822**	1			
6. Physical activity baseline (weekdays)	-0.400**	-0.387**	0.641**	0.491**	0.667**	1		
7. Physical activity follow-up (weekdays)	-0.332*	-0.344**	0.419**	0.681**	0.619**	0.711**	1	
8. Physical activity sum (baseline plus follow-up) (weekdays)	-0.397**	-0.396**	0.579**	0.628**	0.696**	0.933**	0.916**	1
Females (n = 117)	1	2	3	4	5	6	7	8
1. Fat mass baseline	1							
2. Fat mass follow-up	0.941**	1						
3. Physical activity baseline (weekends)	-0.266*	-0.338**	1					
4. Physical activity follow-up (weekends)	-0.277*	-0.304*	0.564**	1				
5. Physical activity sum (baseline plus follow-up) (weekends)	-0.307*	-0.364**	0.895**	0.873**	1			
6. Physical activity baseline (weekdays)	-0.319*	-0.335**	0.578**	0.507**	0.615**	1		
7. Physical activity follow-up (weekdays)	-0.336**	-0.339**	0.460**	0.797**	0.702**	0.631**	1	
8. Physical activity sum (baseline plus follow-up) (weekdays)	-0.362**	-0.373**	0.575**	0.721**	0.729**	0.904**	0.902**	1

The numbers (1 to 8) in the first line mean each variable of exposures, mediators and outcomes inserted in the correlation model (shown in numerical order in column 1). *P < 0.05; **P < 0.001.

patterns[19] and physical activity.[20] Among the domains of physical activity, leisure-time is most associated with reduction of body fat and improvements in metabolic profile, especially when exercise is included,[6] given that this generally has sufficient intensity to promote health gains.

We found that even though physical activity during weekends (but not weekdays) had a low effect, it partially mediated the association between fat mass at the baseline and at the follow-up, thus promoting a protective effect (reduction of body fat). This is an important issue, given that only physical activity performed during weekends, with a relatively small follow-up period, was a high stable factor (body fat). Therefore, physical activity during weekends can be a protective factor, especially if other healthy behaviors during weekends are taken into consideration. Energy intake, especially through carbohydrates and fat, is usually high during weekends.[21] Therefore, a greater level of physical activity could attenuate the association between poorer dietary patterns and obesity. Another factor that can contribute to obesity on weekends relates to sleep patterns: people generally sleep for longer times than on weekdays.[22] The reduction of energy expenditure during weekends could be attenuated by a greater level of physical activity.

From another point of view, the correlation between physical activity during weekdays and weekends was high, such that the subjects with higher physical activity levels during weekends also had higher physical activity during weekdays. Therefore, the homogeneity of physical activity levels during weekdays could also explain why there was an association with physical activity during weekends but not with physical activity during weekdays. In addition to the well-recognized fact that physical activity may be attenuated during weekends, given the level of occupation during weekdays, weekend physical activity could thus be an alternative, bearing in mind that even if physical activity levels during weekends might not meet the recommendations, a greater level of physical activity during weekends can be a protective factor against obesity and all-cause mortality.[10,11]

This is a special issue in relation to our sample, which was composed of university staff who were working for eight hours per day during the week. In this regard, our study shows clear practical implications, through confirming that high levels of physical activity during weekends seem to be a good strategy for reducing body fat. However, these data should be interpreted with caution. Even with the evidence showing that greater levels of physical activity during weekends can be considered to be a protective factor against obesity, shown in our study, and against mortality, shown in previous studies,[10,23] some types of activity may be dangerous when done only during weekends. This is especially so in relation to high-intensity activities, which increase the chance of injuries.[24]

Our study has limitations that need to be pointed out. Considering the missing data and dropout rate, the sample of our study was reduced in size by 29.7% between the baseline and follow-up measurements. A larger sample size would have given rise to lower risk of bias of the results. The measurement of physical activity using a pedometer was objective, but it only took into account steps and did not assess the intensity of physical activity.[25] Moreover, our study did not include potential confounders such as sleep and dietary patterns, which could be potential moderators in the models.[21] In the analyses, although we made adjustments according to sex, the sample was not divided into subgroups according to sex, to be analyzed.

On the other hand, we made use of a good indicator of body fat levels (DXA)[26] and presented data from a 12-month follow-up regarding the effect of objectively measured physical activity on body fat among adults. We assume that this was a point of strength in this study.

CONCLUSION

In summary, physical activity during weekends partially mediated the association between fat mass at baseline and fat mass after one year of follow-up among adults. Furthermore, future studies should investigate the joint associations between

Table 5. Mediation models for different physical activity levels during weekdays and weekends and the association with fat mass at baseline and fat mass at follow-up (one year)

	Total effect β (95% CI)	Controlled direct effect β (95% CI)	Natural indirect effect β (95% CI)	E-value RR
Weekdays				
Baseline physical activity	0.972 (0.930 to 1.014)	0.963 (0.919 to 1.007)	0.009 (-0.007 to 0.023)	1.097
Follow-up physical activity	0.972 (0.930 to 1.014)	0.962 (0.919 to 1.006)	0.009 (-0.004 to 0.023)	1.102
Baseline + follow-up physical activity	0.972 (0.930 to 1.014)	0.961 (0.916 to 1.005)	0.011 (-0.005 to 0.027)	1.112
Weekends				
Baseline physical activity	0.972 (0.930 to 1.014)	0.951 (0.908 to 0.994)	0.021 (0.005 to 0.036)	1.158
Follow-up physical activity	0.972 (0.930 to 1.014)	0.957 (0.914 to 1.000)	0.015 (0.001 to 0.028)	1.130
Baseline + follow-up physical activity	0.972 (0.930 to 1.014)	0.948 (0.904 to 0.991)	0.024 (0.008 to 0.041)	1.174

Adjusted for chronological age, sex and race.
CI = confidence interval; RR = risk ratio.

dietary patterns, sleep time, physical activity during weekends and body fat. Considering the clinical implications, stimulation of habitual physical activity (i.e. increasing the number of steps per day) is a simple, cheap and efficient tool for reducing the fat mass over one year, especially on weekend days.

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Alcohol use and risk of vehicle accidents: cross-sectional study in the city of São Paulo, Brazil

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ABSTRACT

BACKGROUND: Harm to other people caused by an individual under the influence of alcohol (UIA) can occur in a variety of relationship situations between the drinker and these other people.

OBJECTIVES: To estimate the prevalence of the risk of vehicle accidents (RVA) involving people who are UIA, according to sociodemographic variables, respondent alcohol use and gender.

DESIGN AND SETTING: Cross-sectional study, in which a household survey was carried out on a cluster-stratified representative sample of urban residents in the city of São Paulo.

METHODS: The final sample was composed of 1,155 subjects aged 18-59 years, who were interviewed using the GENACIS Harm-to-Others questionnaire. Individuals were defined as having been harmed if an affirmative response was given to at least one of the questions that refers to RVA involving people who had been UIA in the last twelve months. Post-stratification weights were calculated to adjust for the study design and for no response. Since the outcome was binary, logistic regression was used in multivariable analysis.

RESULTS: The final response rate was 58.6%. The overall prevalence of RVA was 13.6% (95% confidence interval, CI 11.0-16.7): 16.6% among men and 10.8% among women. After the logistic regression, age remained as a protective factor (odds ratio, OR 0.95) and binge drinking as a risk factor (OR 2.03).

CONCLUSION: This study showed that binge drinking was associated with RVA.

INTRODUCTION

Harm to other people caused by individuals who are under the influence of alcohol (UIA) can happen in many ways, to different degrees and to people with different relationships with the drinker. Harm to other people due to alcohol consumption can include intentional or unintentional injury and can affect a whole group or single individuals, who may be spouses, relatives, friends, non-relatives living in the same home, co-workers or even strangers.[1-3]

Studies have shown that traffic accidents and alcohol consumption are directly related, thereby causing serious consequences to individuals, families and the community.[4-8] Brazil is one of the countries with the highest rates of traffic accidents relating to alcohol consumption, with huge social costs.[4-8] A recent review by Araújo et al.[9] assessed several studies on traffic accidents and alcohol use in Brazil, and showed that there was high prevalence of alcohol use and an association between this and the severity of injuries. A Brazilian survey conducted in 2012 indicated that the prevalence of individuals who reported driving after consuming alcohol in the last year was 27.3% among men and 7.1% among women.[10]

Epidemiological studies evaluating alcohol use relating to fatalities in the state of São Paulo, the Federal District and the city of Porto Alegre found alcohol in the blood in 45%, 43% and 32% of the subjects, respectively. Among non-fatal accident victims treated in trauma and emergency care centers in Uberlandia, state of Minas Gerais, 31.8% of these patients tested positive for blood alcohol content, and they more frequently required hospitalization (70.4% versus 37.9%; $P < 0.05$).[11,12]

A study carried out in the city of Rio de Janeiro showed that 42.5% of fatal traffic accidents involved individuals with some level of blood alcohol concentration, among which 66.2% had levels between 0.6 and 2.0 g/L of alcohol in the blood. Four to eight doses of alcohol, on average, in the last hours before the accident may indicate excessive alcohol consumption. However, this study in Rio de Janeiro found that the frequency of blood alcohol tests was low: only 34.8% of

all victims of traffic accidents underwent the test. This will have contributed to underreporting of the true numbers of alcohol-related accidents in traffic.[13]

A cross-sectional study developed in the emergency services of Brazilian state capitals and in the Federal District showed that among the cases from traffic accidents that were attended, especially those involving motorcycles, the proportion in which alcohol consumption was a factor ranged from 5.8% in Rio de Janeiro to 28.6% in Teresina (state of Piauí).[14] The city of São Paulo, the setting of the present study, is situated in the southeastern region of Brazil, which is the region of this country with highest lifetime rate of alcohol use (80.4%).[15]

In 2008, the Brazilian Congress approved law no. 11.705/2008, which reduced to zero the level of alcohol in blood that was permitted for drivers in this country.

The current study is part of GENAHTO, an acronym for Gender and Alcohol's Harm to Others.[16] "GEN" signifies the importance of gender in studying the harm that alcohol causes to other people, along with the project's continuity with the GENACIS Project (Gender, Alcohol and Culture: an International Study). In the latter, several cross-sectional studies carried out in different countries had the aim of evaluating the patterns of alcohol use between men and women in different contexts and cultures, from a gender perspective.[3,17]

GENAHTO analyses are guided by a conceptual model in which the harm that alcohol causes to other people is examined within a nested multi-level set of potential influences. The central aspect of these analyses is the characteristics of individuals experiencing and causing this harm, such as gender and drinking patterns. These characteristics are entrenched in the individual's role relationships, social groups and drinking contexts and provide extensive data on harms due to others' drinking, from the victim's perspective.[16] GENAHTO aims to contribute towards elaboration of preventive and interventional measures for problems relating to use of alcohol by men and women. Through this contribution, measures that are sensitive to gender issues and policies regarding alcohol use can be developed. This research is carried out through a standardized questionnaire, with adaptation to different cultures.

OBJECTIVE

The aim of the present study was to estimate the prevalence of the risk of vehicle accidents (RVA) involving people who were UIA, according to sociodemographic characteristics and respondent alcohol use.

METHODS

Sample

This study comprised a cross-sectional survey of the general population that was carried out on a cluster-stratified representative sample of urban residents of the city of São Paulo. The participants were aged 18 to 59 years. The sample was probabilistic.

Stratified sampling procedures were used in three stages: census tract, household and resident. Considering that only one resident in each household would be interviewed, 1,250 households were included in the sample. These households were distributed in 50 census tracts. In each census tract, 25 households were surveyed and, in each household, a single resident. To select this resident, we used the procedure proposed by Kish.[18] Considering that empty dwellings would be found and that the refusal rate among the residents was likely to be 20%, 1,600 households were drawn, i.e. 32 in each census tract. If the home was found to be unoccupied, a maximum of two further visits were made, to try to find a resident. The interviews were conducted between September 2014 and January 2015. The percentage of the households that received the interviewers was 71.0%, but 17.5% of the households refused to participate, which resulted in a final response rate of 58.6%.

Setting

The study site was the city of São Paulo, which is the capital of the state of São Paulo. This is the largest and the most populated city in Brazil and in the southern hemisphere. The Brazilian Institute for Geography and Statistics calculated the population of this municipality as 11,253,503 inhabitants in 2010. In this city, there were over 8.5 million registered motor vehicles in 2017; in 2016, there were 16,052 accidents, with 19,235 victims, including both fatal and non-fatal cases.[19,20]

Dependent variable: risk of vehicle accidents (RVA)

RVA was the dependent variable in this study. Individuals were defined as having been harmed if an affirmative response was given to at least one of the questions referring to vehicle accidents that involved people who were UIA, in the last twelve months. The dependent variable was constructed through the following questions:

- Have you ever been a passenger of a driver who had drunk a lot?
- Have you had a car accident (or other motor vehicle accident) because of someone else's drinking?
- Did you feel at risk in the car when someone else was driving, because of how much the person had drunk?
- Were you injured in a car accident because of how much someone else had drunk?

Independent variables

The instrument used for data-gathering was the GENACIS Harm-to-Others questionnaire (available upon request):

- Sociodemographic variables
  All sociodemographic characteristics, including the variables of gender, age, color, income and education were included in this study and were assumed to be independent for the analysis.

- Respondent alcohol use

  The respondents were questioned about their alcohol consumption. They were classified as abstinent (had never made use of alcohol in their lifetime), former drinker (had not used alcohol in the last 12 months) or current drinker (had had alcohol intake in the last 12 months. The drinkers reported their consumption in terms of quantity and frequency on a typical day. Binge drinking was also investigated, and this was considered to consist of consumption of four or more drinks for women and five or more drinks for men on one occasion in the last 12 months. For the analysis, the number of doses on a typical day, any occurrences of binge drinking and the score from the alcohol use disorders identification test (AUDIT) were included, for current drinkers only.
- AUDIT

  The AUDIT[21] is an instrument with 10 items that was designed to identify the patterns of alcohol use. It has been validated for use in Brazil.[22] When respondents get a score of eight points or more, their consumption is considered to be at a problematic level of use. Although this test includes questions that identify binge drinking, its aim is to identify subjects who already present a problematic pattern of use, as defined by this instrument.

Analytical model

Associations between the outcome and independent variables were evaluated using the Rao-Scott test.[23] Each observation was weighted accordingly to compensate for the effects of delineation and of no response. Firstly, we ran bivariate analyses, to select eligible variables for inclusion in multivariable analysis. We used multivariable logistic regression analysis, with backward stepwise variable selection.[24] All the variables that showed associations with outcome presenting $P \leq 0.25$ were included in the models.

The results from these analyses are presented in the form of odds ratios (OR), using 95% confidence intervals (CI). Only variables for which the associations presented $P < 0.05$ were retained in the final model. We did separate analyses for men and women. The data were analyzed using the Stata 12.0 statistical software (StataCorp LP, College Station, TX, USA).

Ethics

The proposal for this study was approved by the Research Ethics Committee of the Medical School, Universidade Estadual Paulista (UNESP), on November 5, 2012 (protocol no. 4410-2012), and was supported by the Research Support Foundation of the State of São Paulo Research Program for the National Health System (Fundação de Amparo à Pesquisa do Estado de São Paulo-Programa de Pesquisa para o SUS, FAPESP-PPSUS) (grant number 2012/51237-8).

RESULTS

The final sample was composed of 1,155 subjects, among whom there were 648 women (52.3%) and 507 men (43.7%). The final response rate was 58.6%. The prevalence of RVA was 13.6% (95% CI 11.0-16.7%) and it was significantly higher among men (P = 0.01): 16.6% among men (95% CI 12.0-21.2%) and 10.8% among women (95% CI 8.1-13.5%).

As mentioned earlier, bivariate analysis was run for each gender. Regarding demographic variables (**Table 1**), exposure to RVA due to alcohol use by other people was significantly higher among

Table 1. Risk of vehicle accidents involving people who were under the influence of alcohol in the last 12 months, according to sociodemographic characteristics (n = 1,155), city of São Paulo, 2014

Sociodemographic characteristics	Risk of vehicle accidents Males (n = 507)			Risk of vehicle accidents Females (n = 648)		
	n	%	P*	n	%	P*
Age			**< 0.001**			0.72
< 30	41	29.0		20	12.4	
30 to 49	37	12.9		33	9.9	
≥ 50	4	4.0		12	10.6	
Color			0.83			0.68
White	33	17.1		34	11.4	
Nonwhite	49	16.2		31	10.2	
Marital status			**0.004**			0.25
Married	28	10.5		28	9.1	
Widowed/divorced/ separated	6	14.4		12	9.7	
Single	48	24.4		25	13.5	
Education			**0.04**			0.20
Only elementary school	4	8.7		11	11.0	
Incomplete high school to incomplete college/ university	55	20.3		40	12.7	
Completed college/ university or more	23	12.8		14	6.6	
Children			**0.01**			0.79
Yes	36	11.2		46	10.6	
No	46	22.9		19	11.2	
Current work status			**0.03**			0.62
Employee or self-employed	66	15.5		44	11.2	
Retired	1	7.1		2	15.9	
Unemployed	11	21.2		11	12.1	
Student	4	46.6		2	14.2	
Housekeeper	0	0		6	5.9	
Monthly family income			0.82			0.77
0 to 3 minimum wages	47	16.5		45	10.9	
> 3 minimum wages	33	15.6		16	10.1	
Education level of the person responsible for family income			0.45			**0.01**
Only elementary school	26	12.5		12	5.1	
Incomplete high school to incomplete college/ university	40	18.1		42	14.0	
Completed college/ university or more	13	19.3		11	11.6	

*Rao-Scott test. Percentages were calculated considering weights for non-response and for study design.

the following groups of men: those who were younger (29.0%), single (24.4%), with schooling levels ranging from incomplete high school to incomplete college/university (20.3%), with no children (22.9%) and students (46.6%). Among women, only the education level of the person responsible for the family income was significant (P = 0.01). RVA was most prevalent among individuals whose schooling level ranged from incomplete high school to incomplete college/university (14.0%).

As shown in **Table 2**, among men, occurrences of vehicle accidents involving people who were UIA in the last 12 months were associated with being a current drinker (19.2%). It is noteworthy that, for this variable, a dose-response effect could be seen among lifetime abstainers, former drinkers and current drinkers. In addition, reporting occurrences of consumption of five or more alcoholic beverages on a single occasion in the last 12 months (26.2%), consuming five or six drinks on a typical day (30.3%) and AUDIT scores of eight or more points (29.2%) were associated with RVA.

Among women, occurrences of vehicle accidents involving people who were UIA in the last 12 months were associated with being a current drinker (16.3%) and high frequency of alcohol consumption in the last 12 months (P = 0.001).

For the multivariable analysis, it was decided to build a single model for both genders together. All the variables selected were included in the model and they were retained if P > 0.05. In order to highlight the importance of binge drinking, we presented two models (**Table 3**). In the first model, only gender and age were included, and this showed the risk associated with male gender (OR = 1.64) and the protective effect of increasing age. In the second model, binge drinking was included and this nullified the risk associated with male gender. It was observed that the binge drinking variable was a risk factor (OR = 2.38) and that its introduction changes the OR values for gender, thus changing its significance. Also, the inclusion of binge drinking did not prejudice the role of age, which remained a protective factor.

Table 2. Risk of vehicle accidents involving people who were under the influence of alcohol in the last 12 months according to alcohol consumption and according to gender, city of São Paulo, 2014

Risk factor	Risk of vehicle accidents Males (n = 507)			Risk of vehicle accidents Females (n = 648)		
	n	%	P	n	%	P
Alcohol consumption			**0.008**			
Abstinent	1	1.5		11	5.7	
Former drinker	13	14.6		10	5.6	**0.0001**
Current drinker	68	19.2		44	16.3	
Frequency of alcohol consumption in the last 12 months			0.35			
Never	14	10.7		21	5.6	
Monthly or less	13	19.8		15	14.9	
2 to 4 times per month	46	18.6		28	17.9	**0.001**
2 to 3 times per week	3	17.9		0	0	
4 or more times a week	6	26.0		1	15.6	
Binge drinking[a,b]			**0.0002**			
No	15	9.7		18	13.6	0.17
Yes	53	26.2		26	19.8	
Drinks on a typical day[a]			**0.03**			
1 to 4	34	15.0		29	14.1	
5 to 6	13	30.3		7	27.6	0.10
7 to 9	9	29.3		3	39.9	
≥ 10	12	28.7		5	31.1	
AUDIT score ≥ 8[c]			**0.0002**			
No	25	12.7		27	14.4	0.10
Yes	43	29.2		17	25.2	

AUDIT = alcohol use disorders identification test.
Percentages were calculated considering weights for non-response and for study design. [a]Information only among drinkers; [b]Four or more drinks for women and five or more drinks for men on one occasion in the last 12 months; [c]Alcohol use identification test.

Table 3. Logistic regression for risk of vehicle accidents involving people who were under the influence of alcohol in the last 12 months, city of São Paulo, 2014 (n = 1,155)

	Crude odds ratio	Confidence interval	Adjusted odds ratio	Confidence interval	P
Model 1					
Age	0.96	0.94-0.98	0.96	0.94-0.98	**< 0.001**
Gender					
Female	1	-	-	-	
Male	1.64	1.11-2.41	1.61	1.13-2.32	**< 0.01**
Model 2					
Age	0.96	0.94-0.98	0.95	0.93-0.98	**< 0.001**
Sex					
Female	1	-	-	-	
Male	1.64	1.11-2.41	1.11	0.75-1.66	0.60
Binge drinking[a]	2.38	1.53-3.71	2.03	1.26-3.25	**0.004**

[a]Four or more drinks for women and five or more drinks for men on one occasion in the last 12 months.

DISCUSSION

Social harms from drinking are inherently interactional. For social harm to be recognized as occurring, there needs to be not only drinking behavior that is seen as problematic, but also a reaction by someone other than the drinker. The harm may occur to the drinker or to other people.[25] Alcohol surveys have usually asked drinkers themselves about problems from their own drinking. However, it is important to investigate people who have been harmed by other people's drinking.[26]

The total percentage of individuals who reported occurrences of RVA in the present study was 12.73%. Using data from the 2014 to 2015 United States National Alcohol Survey, Karriker-Jaffe et al.[27] found that fewer than 1% of the respondents had been in traffic accidents caused by someone who had been drinking, in the last year.

The main outcome of the present study was that a significant association was found between higher prevalence of risks of vehicle accidents (RVA) and binge drinking, caused by other people's consumption. In other words, when drinkers practice binge drinking, they put themselves at risk, regardless of whether or not they are the driver. A causal link has been shown between consumption of alcoholic beverages and occurrences of traffic accidents, considering the effects of alcohol on individuals' perception, vision, reflexes, consciousness and behavior.[28] A study conducted in all Brazilian state capitals and the Federal District showed that the percentage of the subjects who had consumed any amount of alcohol before driving was 5.3% in 2011 and 7.3% in 2016.[29] The first National Household Survey on Alcohol Consumption Patterns, which was applied in 143 Brazilian cities between 2005 and 2006, indicated that 34.7% of motorists drank and drove in the last 12 months.[6] Data from 2008 for the adult population of 27 cities showed that 1.5% of individuals reported having driven a motor vehicle after excessive alcohol consumption, on at least one occasion in the last 30 days.[7] One study found that 41.2% of the 431 victims of fatal motor vehicle accidents over 16 years of age who were admitted to the Institute of Legal Medicine of the Federal District (IML-DF) presented a blood alcohol concentration above 0.6 g/l.[11]

In the present study, it was observed that age was a protective factor, such that RVA decreased with increasing age. The practice of driving after excessive alcohol consumption showed highest frequency in the 25 to 34-year age group (4.0% among men and 0.7% among women).[7] Duailibi et al.[8] studied drivers between 21 and 30 years old, on weekend nights in Diadema (SP) and observed that more than 20% of the drivers undergoing the breathalyzer had breath alcohol levels above 0.01 g/dl.

In Brazil, violent deaths, including homicides, traffic accidents and suicides represent about 70% of deaths among people between 15 and 24 years of age. This number places Brazil among the 10 countries where traffic accidents are responsible for more than 60% of deaths.[30]

Brazilian data from the telephone-survey surveillance system for risk factors and protective factors relating to chronic diseases (Sistema de Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquerito Telefônico, VIGITEL) for the period from February to December 2016 showed that the rate of alcohol abuse had increased from 15.7% to 19.1% over the preceding ten-year period.[29] The second National Survey of Alcohol and Drugs, conducted among individuals aged 14 years and over, investigated consumption rates of five doses or more for men and four doses or more for women, on a single occasion within a period of up to 2 hours, in the last 12 months. The data showed prevalences of 45% in 2006 and 58% in 2012, i.e. increasing from 54% to 66% among men and from 34% to 48% among women.[10]

Although gender did not remain significant after multivariable analysis in the present study, data in the literature show that men are more likely than women to binge-drink and to drive after doing so. Data from a telephone survey among adults in the United States aged 18 years and over found that 75.1% of binge drinkers were men and that 49.7% consumed seven or more drinks during their most recent binge-drinking episode. In the gender-based assessment, men were more likely than women to drive after binge drinking (13.2% versus 8.1%), and men accounted for 82.9% of all recent binge drinking and driving episodes.[31]

In the 60th World Health Assembly in 2007, binge drinking was shown to be responsible for 3.7% of deaths and was associated with 4.4% of diseases in the world. Thus, binge drinking is a public health problem and monitoring it is essential in order to find out about consumption patterns and ascertain which segments of the population are more vulnerable. These data are fundamental for formulating and funding public policies for health promotion and prevention of risky behavior.[32]

One possible limitation of the present study was the higher non-response rate among men and especially in census tracts with middle-to-high income. Higher non-response rates can be expected in large urban centers, especially in those with high incidence of violence and fear of this situation. However even developed countries can have low response rates: in a similar study carried out in Ireland, the response rate was 37%; while in Australia it was 38%.[16] There is no consensus regarding the minimum response rate for population surveys, taking into account the characterization of non-responders, or regarding the extent to which this loss relates to the information sought by the study. Since the subject of RVA is a sensitive issue, we can assume that there is a risk minimization factor: probably the risk is greater than what has been found.

Our data differ from those of some other studies that indicated high abstinence rates in Brazil, especially in populations with lower levels of education.[33,34] It is possible that this result is related to the questionnaire that was used. The GENACIS Harm-to-Others questionnaire assesses the frequency of alcohol consumption through detailed questions about different types of alcoholic beverages, with the aim of minimizing biases in memory, misrepresentation, false responses or non-acceptance, which are common in surveys on embarrassing or intimate issues.

Nonetheless, the figures obtained in the present study are close to the national data, which indicate that the prevalence of drinkers is around 50%.[10] Also, as previously mentioned, the city of São Paulo is characterized by a peculiar situation, in that it is located in the region with highest lifetime rate of alcohol use (80.4%).[15]

The strengths of this study, on the other hand, are that it was conducted over a short period, was stratified according to neighborhoods and had a representative sample of residents of the city of São Paulo, between 18 and 59 years of age. Thus, the results can

be generalized to other large urban centers and probably do not reflect the patterns of rural areas of Brazil.

The problems arising from consumption of alcoholic drinks by drivers have been studied internationally in a broad manner. In Brazil, the risk of vehicle accidents associated with alcohol use can be considered to be a major public health problem, with a major impact on morbidity and mortality, especially in the young male population. Therefore, preventive interventions need to focus on these problems, for instance through promoting strict enforcement of drinking and driving laws to prevent this combination of behaviors.

CONCLUSIONS

GENAHTO is the first project to assess the harm that alcohol use causes to other people in diverse societies.[16] The current study aimed to estimate the prevalence of the risk of vehicle accidents involving people who were under the influence of alcohol, and it attempted to fill the gap regarding the lack of studies on people who are victims in accidents involving alcohol consumption by other people. It is important to highlight that we found that individuals who practiced binge drinking put themselves in RVA situations, regardless of whether they are the driver or not. Until now, this impact has not been considered in establishing public policies regarding alcohol consumption. This indicates that there is a need for further studies in this important area, and the results from the present study could be useful for guiding preventive strategies.

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AOP

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Risk factors associated with drug therapy among elderly people with Alzheimer's disease: a cross-sectional study

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ABSTRACT

BACKGROUND: Improving knowledge and establishing strategies and policies for better patient safety are worldwide priorities.

OBJECTIVE: To evaluate drug safety among elderly people with Alzheimer's disease (AD).

DESIGN AND SETTING: Cross-sectional study among elderly people within the National AD Assistance Protocol (PCDTDA/MS) who were living in the municipality of Araraquara, Brazil, in 2017.

METHODS: Through interviews conducted with relatives/caregivers of elderly people with diagnoses of AD, the following variables were evaluated: comorbidities, drug therapy used, use of potentially inappropriate medications for the elderly (PIMs), presence of potentially inappropriate interactions (PIIs) and medication regimen complexity index. Factors associated with AD severity were also evaluated. Multivariate and simple logistic regressions were applied.

RESULTS: 143 elderly people enrolled in PCDTDA/MS were analyzed. The majority were women (67.1%); assisted only through the public healthcare system (75.5%); polymedicated (57.4%); using at least one PIM (63.6%); presenting at least one PII (63.6%); and under drug therapy of low to medium complexity (92.2%). No semi-annual monitoring of the effectiveness of PCDTDA/MS drugs was identified. The proportion using AD drug therapy at daily doses differing from those recommended by the World Health Organization was 75.6%. However, these doses were not associated with drug risk.

CONCLUSION: The data from this study raise the hypothesis that use of polypharmacy might show a correlation with severity of AD. The drug safety risk may be associated with comorbidities of the metabolic syndrome, anxiety and off-label use of PIMs, such as risperidone and quetiapine, and benzodiazepines (i.e. clonazepam and flunitrazepam).

INTRODUCTION

Prescription of potentially inappropriate medications for the elderly (PIMs),[1] the complexity of drug therapy regimens,[2] the risk of potentially inappropriate interactions (PIIs),[3] use of polypharmacy[4] and occurrences of adverse drug events (ADEs)[5] are factors that compromise drug safety among elderly people.

The risk of hospitalizations due to ADE is two to seven times greater among elderly people.[6] It has been estimated that for every two hospitalized elderly individuals, the reason for admission of one of them was possibly an occurrence of one or more ADEs.[7]

PIMs are drugs with risks that can outweigh the benefits, especially when there are safer and more effective alternatives.[8] They are also associated with occurrences of ADEs,[9] and their use contributes to a twofold increase in the risk of hospitalization among elderly people.[10]

In addition, some drugs that have been standardized as essential by the World Health Organization (WHO) and in the Brazilian National List of Essential Medicines (RENAME-Brazil) are considered to be PIMs. However, there is often no other safer drug alternative.[11]

With the aging of the population, there are projections of high prevalence and incidence of dementia,[12] among which Alzheimer's disease (AD) is the most prevalent form.[13] However, within the context of drug therapy for these conditions, we are not aware of any study on such therapy with concomitant evaluation of drug risk factors, i.e. polypharmacy, PIM use, PII, drug therapy complexity index and comorbidities. Nor have associations of these factors with disease severity among elderly people with dementia or AD been assessed.[14-17]

OBJECTIVE

The objectives of the present study were to characterize elderly people with a diagnosis of AD; identify comorbidities, drug therapy complexity, use of PIMs and presence of PIIs; and raise hypotheses regarding possible drug risk factors. Through this, we aimed to contribute to national and international patient safety goals.

METHODS

Study design and ethics

A cross-sectional study was conducted in Araraquara, Brazil, over the course of the year 2017.

The study design was based on the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[18] The protocol for this study was approved by the Research Ethics Committee of the Universidade Federal de São Paulo in 2016 (no. 2.877.560).

Setting and participants

The study was conducted at the Araraquara Reference Center for Elderly Patients (CRIA) and at the Regional Health Directorate III (DRS-III) for services of specialized nature.

Elderly individuals with a diagnosis of AD are referred by the healthcare services to the CRIA. CRIA provides medium-complexity services and specializes in geriatric care, using protocols for treating forgetfulness, dementia, stroke sequelae and mild depression.

In DRS-III, drug therapy for AD is dispensed. In 2017, 260 elderly people were registered at the DRS-III of Araraquara within the Clinical Protocol and Therapeutic Guidelines for Alzheimer's Disease of the Ministry of Health (PCDTDA/MS),[19] including both new and old cases.

These guidelines are documents based on scientific evidence that establish criteria for diagnosing the health problem and make recommendations for treatments and dosages and for monitoring the therapeutic results.

The elderly people who were registered within the PCDTDA/MS had been diagnosed with AD (ICD-10: G30) in accordance with the criteria of the National Institute on Aging and the Alzheimer's Disease and Related Disorders Association, which have been endorsed by the Brazilian Academy of Neurology.[20]

AD is diagnosed through the following procedures: evaluation of the clinical history; cognitive screening through the clinical parameters of the Mini-Mental State Examination (MMSE)[21] and the Clinical Dementia Rating (CDR);[22] laboratory tests (vitamin B12, folic acid, electrolytes, blood glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase and thyroid-stimulating hormone); and magnetic resonance imaging or computed tomography scans.[19]

In addition, the drug therapy that has been approved for treating AD, i.e. donepezil, galantamine and rivastigmine (acetylcholinesterase inhibitors) and memantine, is available free of charge to elderly patients who are included in the PCDTDA/MS. AD drug therapy dispensing is performed through the public healthcare system in order to ensure access and integrality of the treatment at the outpatient level.

Thus, elderly individuals who had been registered within the PCDTDA/MS were included in this study. Elderly individuals who were living in long-term institutions were excluded for ethical reasons, given the advanced stage of their disease and the absence of a relative or caregiver to participate in the interview.

Data

This study was conducted through interviews with relatives or caregivers of elderly patients who were seen at CRIA and at the time of dispensing of AD drug therapy in DRS-III. The interview was led by one researcher.

A standardized questionnaire was drawn up for the interviews, and it sought the following information about the elderly subjects: gender; access to healthcare (only through the public healthcare system, only through the private system or through a mixture of the public and private systems); age; body mass index (BMI); schooling; monthly income; time of diagnosis of AD; family history of AD; severity of AD; clinical parameters (MMSE[21] and CDR[22]); drug therapy and time of use; medication regimen complexity index (MRCI); defined daily dose (DDD) of AD drug therapy, stratified as above the requirement, below the requirement or adequate dose, as defined by WHO; comorbidities and time of diagnosis; and consumption of alcohol and tobacco.

The data obtained through the interview were confirmed using secondary sources, i.e. from medical records available at the healthcare service, prescriptions and clinical laboratory tests on the elderly subjects.

Measurements

Comorbidities

Comorbidities were identified through the relatives' or caregivers' reports or through self-reports; and from secondary data sources (medical records).

Severity of Alzheimer's disease

The severity of Alzheimer's disease was assessed through insertion of memantine either in association with anticholinesterases or as monotherapy. The insertion of memantine was evaluated to ensure that this was not associated with anticholinesterase intolerance, but rather with the severity of AD, in accordance with the MMSE and CDR scores that had been pre-established within the PCDTDA/MS.[19]

Metabolic syndrome

Metabolic syndrome (MetS) consists of a set of factors that increase the risk of coronary heart disease.[23]

The guidelines developed through the National Cholesterol Education Program for detection of MetS recommend measurement of abdominal circumference, blood glucose levels, cholesterol levels (LDL and HDL) and blood pressure.[23] However, since it was not possible to make these measurements in this study, the following criteria were used to define MetS: BMI of 30 kg/m^2 or greater) and use of antihypertensives antidiabetics and antidyslipidemics, as recommended in the literature.

Thus, presence of MetS was ascertained in terms of the presence of at least three of the factors described above.

Medication regimen complexity index (MCRI)

The complexity of drug therapy results from the multiplicity of prescribed regimen factors.

The MRCI is an open index divided into three domains: dosage form (pharmaceutical form according to route of administration), dosing frequency (number of times the drugs is given per day/week/month) and administration instructions (i.e. tablet fractionation, fasting, etc.).[24] The more complex the dosage schedule and the process of drug use are, the higher the score assigned will be.

The minimum score is 1.5 points, which represents a single tablet or capsule taken once a day. There is no limit to the number of drugs to be analyzed.

We stratified the MRCI score as denoting low (1.5-14 points), medium (14-28 points) or high complexity (28-42 points).

The MRCI is the gold standard for assessing the complexity of drug therapy.[25] However, it has some limitations, considering that observation of which scores correspond to higher scores shows that there is no maximum score or stratification of these scores. This was the reason why we made our own stratification for this study.

Potentially inappropriate medications

Prescription guides have been developed to identify any use of drugs that is considered inappropriate for elderly individuals. These are termed potentially inappropriate medications (PIMs), i.e. drugs for which the tradeoff between risk and benefit does not justify their use.

In our study, PIM assessments were made through the following prescription guides: updated Beers criteria,[26,27] STOPP/START version 2,[28] French consensus panel[29] and Canadian national consensus panel,[30] and Strand criteria.[31]

These guides report on the drugs that are considered to be PIMs, depending on the clinical condition of the elderly individual, dose, length of time prescribed and PIM-comorbidity interactions.

Drug risk variables

In order to evaluate drug safety among patients with AD, we defined the following variables as drug risk variables: PIM use and PII, evaluated through the updated Beers criteria,[26,27] STOPP/START version 2,[28] French consensus panel[29], Canadian national consensus panel[30] and Strand criteria;[31] the complexity of drug therapy according to the medication regimen complexity index (MRCI);[24] comorbidities identified through self-reports and with confirmation from medical records; and presence of polypharmacy, which was defined as use of five or more drugs for a period greater than or equal to 90 days.

Data analysis

Sample size

Given that a total of 260 elderly people had been registered within the PCDTDA/MS, the sample size for a confidence level of 90% ($\alpha = 0.05$) was 133 elderly people.

Statistical analysis

The variables of interest were described in terms of their absolute and relative frequencies.

Two statistical analyses were conducted: multivariate and simple logistic regressions.

To analyze the severity of AD in relation to the presence of drug risk variables (presence of polypharmacy, high-complexity MRCI, PIM use and occurrence of PII), multivariate logistic regression was used.

From another perspective, to evaluate the influence of each variable of this study on the severity of AD and/or in the presence of one or more variables that had been defined as drug risk variables, simple logistic regression was used. The aim of this analysis was to evaluate whether there were any variables that influenced the severity of AD. For this, AD severity and the drug risk variables were considered to be the dependent variables and the others were independent variables.

Female gender, schooling ≤ 4 years and presence of high-complexity MRCI were defined as independent variables in the simple logistic regression. Individual comorbidities were analyzed, as were comorbidities grouped in accordance with the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

The statistical software used was BioEstat (version 5.3).

RESULTS

Out of the 260 elderly people who were enrolled in the PCDTDA/MS, 16 were excluded because they were living in long-term institutions. Thus, 244 elderly individuals were eligible for inclusion in this study. Fourteen did not agree to participate and there were

another 87 losses, due to the following: AD drug therapy was not received through the public healthcare system (n = 49); AD drug therapy was dispensing to relatives or caregivers who did not know the clinical history of the elderly individual (n = 31); or AD drug therapy was dispensed through a means of transportation that had been hired just to obtain it (n = 7) (**Figure 1**).

The age of the elderly individuals within the PCDTDA/MS ranged from 64 to 97 years. Their median age was 81 years (Q1 = 76; Q3 = 87) and they had had their diagnosis of AD for a median period of four years (Q1 = 02; Q3 = 7.5). Most of these elderly people were women (67.1%); did not have any family history of AD (60.1%); were assisted only through the public healthcare system (75.5%); and had had less than four years of schooling (83.2%). Twenty of these elderly people were illiterate and only six of them had had higher education.

In addition, most of them were polymedicated (57.4%); were making use of at least one PIM (63.6%) and had one PII (63.6%). The mean number of drugs in use was five drugs/elderly person [standard deviation, SD: 2.69] and the drug therapy of 92.2% of these elderly individuals was classified as presenting low or medium complexity.

Furthermore, although diabetes mellitus, arterial hypertension and dyslipidemia were among the most prevalent comorbidities, most of these elderly people did not have metabolic syndrome. However, it was also noted that most of them had one or more of the prodromal symptoms of AD: anxiety, insomnia and depression. These symptoms are frequently treated with drugs that are considered to be PIMs (**Table 1**).

Among the drugs used, which were available through PCDTDA/MS, galantamine (46.1%) and donepezil (33.61%) were the ones most prescribed. Most of the elderly individuals were receiving monotherapy (88%), at daily doses above the defined daily dose that are recommended by the WHO (60.2%) (**Table 2**).

It was noted that no record of MMSE and CDR screening tests has yet been identified, thus making it impossible to evaluate the effectiveness of anticholinesterase treatment. Therefore, no semi-annual reevaluation of the effectiveness of these tests that had been predicted through the PCDTDA/MS was done.

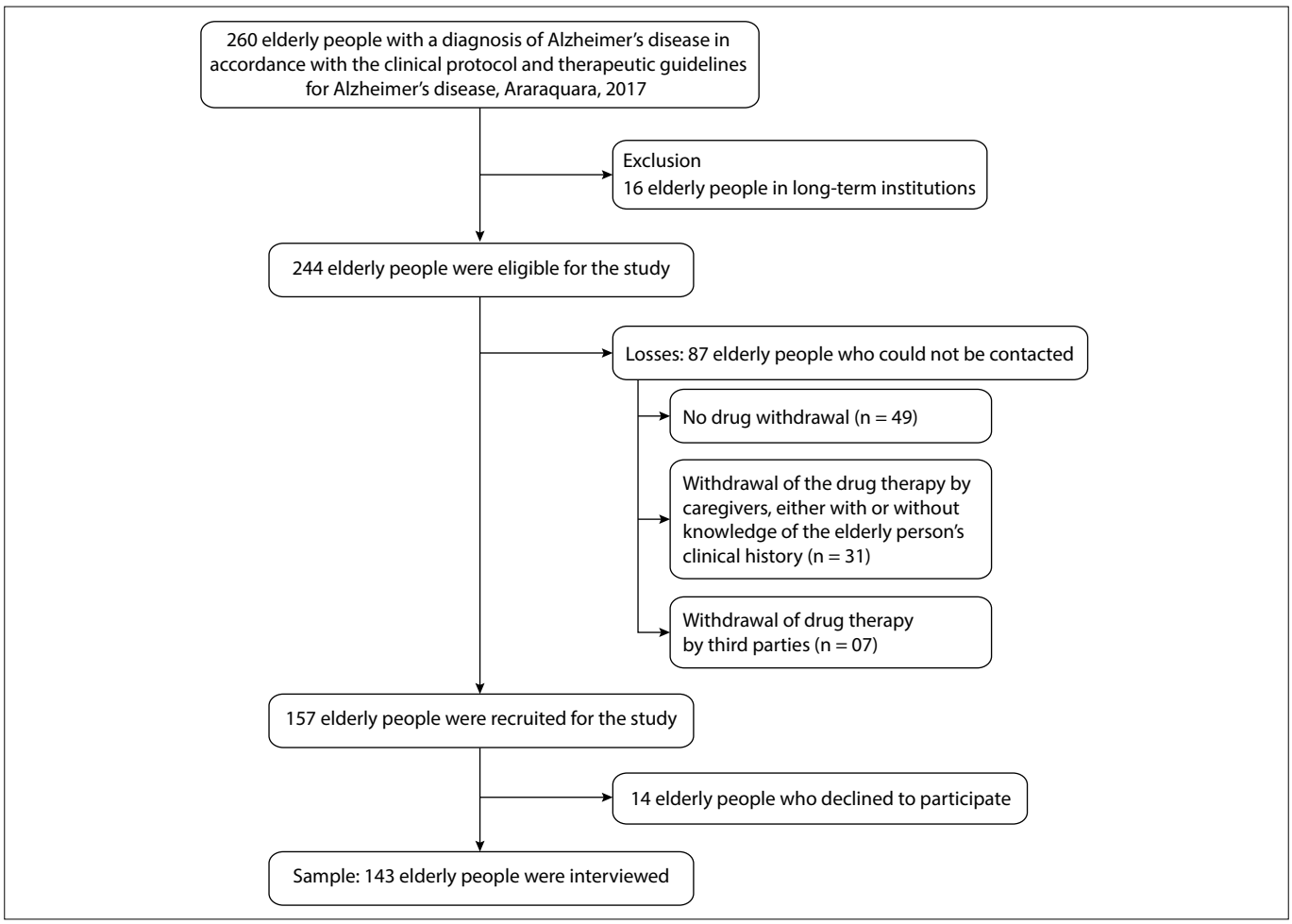

Figure 1. Flowchart of identification and eligibility of elderly people with Alzheimer's disease in accordance with the clinical protocol and therapeutic guidelines for Alzheimer's disease (PCDTDA/MS), in the municipality of Araraquara, 2017.

Table 1. Clinical conditions of the elderly people with probable diagnoses of Alzheimer's disease (n = 143), Araraquara, 2017

Variable	n (%)
Gender	
Female	96 (67.1)
Male	47 (32.9)
Body mass index (kg/m²)	
Median	24.2
Quartile	(Q1 = 21.9/Q3 = 28.3)
Low-weight (< 18)	6 (4.2)
Normal (18-24)	62 (43.3)
Overweight (25-30)	36 (25.2)
Obesity (30-35)	12 (8.4)
Moderate obesity (35-40)	5 (3.5)
Severe obesity (> 40)	1 (0.7)
Without knowledge	21 (14.7)
Drugs in use (n)	
0-1 drug	8 (5.6)
2-4 drugs	53 (37.1)
5-10 drugs	76 (53.1)
> 10 drugs	6 (4.2)
Medication regimen complexity index (MRCI)	
Low	70 (48.9)
Medium	62 (43.3)
High	11 (7.80)
Comorbidities	
Mental and behavioral disorders (ICD)	
Insomnia (F51)	85 (59.4)
Anxiety (F06.4)	81 (56.6)
Depression (F32)	56 (39.2)
Depression without treatment (F32)	9 (6.3)
Schizophrenia (F2054)	2 (1.4)
Panic syndrome (F41)	1 (0.7)
Attention deficit hyperactivity disorder (F90)	1 (0.7)
Diseases of the circulatory system (ICD)	
Arterial hypertension (I10)	77 (53.8)
Stroke (I64)	17 (11.9)
Infarction (I21.9)	8 (5.6)
Angina pectoris (I20)	4 (2.8)
Arrhythmia (I49.9)	4 (2.8)
Endocrine and metabolic diseases (ICD)	
Dyslipidemia (E78)	41 (28.7)
Diabetes mellitus (E11)	35 (24.5)
Metabolic syndrome	23 16.1)
Hypothyroidism (E039)	20 (14.0)
Obesity (E66)	17 (11.9)
Deficiency of cholecalciferol (E55)	10 (7.0)
Nervous system diseases (ICD)	
Epilepsy (G40)	8 (5.6)
Parkinson's disease (G20)	2 (1.4)
Diseases of the musculoskeletal and connective system (ICD)	
Osteoporosis (M81.9)	6 (4.2)
Gout (M10)	5 (3.5)
Osteoarthritis (M19.9)	4 (2.8)
Arthritis (M13.9)	4 (2.8)
Blood diseases and hematopoietic organs (ICD)	
Anemia (D50)	10 (7.0)
Respiratory system diseases (ICD)	
Asthma (J45)	3 (2.1)
Chronic obstructive pulmonary disease (J44.9)	1 (0.7)
Diseases of the genitourinary system (ICD)	
Benign prostatic hyperplasia (N40)	9 (6.4)
Infectious and parasitic diseases (ICD)	
Viral hepatitis C (B18.2)	1 (0.7)
Neoplasms (ICD)	
Prostate cancer (C61)	3 (2.1)
Breast cancer (C50)	2 (1.4)
Others	
Labyrinthitis (H83)	3 (2.1)
Mean number of morbidities/elderly person	4 (SD: ± 2)

ICD = International Classification of Diseases; SD = standard deviation.

Table 2. Description of drug therapy for Alzheimer's disease (AD) and defined daily dose, stratified according to disease stage, among elderly people with a diagnosis of Alzheimer's disease (n = 143), Araraquara, 2017

Drug therapeutic protocol (ATC)	n	Cumulative frequency [%]	DDD (mg)	Dose used/ day (mg)	n (%)
Mild stage of Alzheimer's disease (n = 121)					
Galantamine (N06DA04)	66	46.1	16	8	8 (5.6)
				16	13 (9.0)
				24	45(31.5)
Donepezil (N06DA02)	48	79.7	7.5	5	7 (4.9)
				10	41 (28.7)
Rivastigmine (N06DA03)	7	84.6	9.0	4.5	1 (0.7)
				6.0	6 (4.2)
Moderate stage of Alzheimer's disease (n = 16)					
Galantamine + memantine	10	95.8	-	24 + 20	10 (7.0)
Donepezil + memantine	5	99.3	-	10 + 20	5 (3.5)
Rivastigmine + memantine	1	100	-	4.5 + 20	1 (0.7)
Severe stage of Alzheimer's disease (n = 6)					
Memantine (N06DX01)	6	88.8	20	20	6 (4.2)

ATC = Anatomical Therapeutic Chemical; DDD = defined daily dose; n = number of elderly.

Ninety-one of the elderly subjects (63.6%) used at least one drug that was considered to be a PIM. The mean number of PIMs in use was around two per elderly individual. The incidence of PII was higher among the polymedicated elderly individuals (mean of 2.3 PIIs per elderly person [SD: 1.44]) than among the non-polymedicated individuals (mean of 1.5 PIIs per elderly person [SD: 1.22]).

The most frequently used PIM classes were antipsychotics (44.6%), such as risperidone and quetiapine; and benzodiazepines (BZD) (27.3%), such as clonazepam and flunitrazepam. The most frequent PIIs were of drug-illness type. The largest proportion of PIIs came from use of BZD and Z drugs among elderly people with dementia and depression (41.2%). Additionally, use of antipsychotics without a diagnosis of psychosis (34.5%) stood out (**Table 3**).[26-31]

It was observed that 27.3% [39/143] of the elderly people used benzodiazepine medications for insomnia or anxiety, or as a coadjutant for treating depression, and 3.5% [5/143] used zolpidem for sleep disorders. Therefore, around one in four elderly people used BZD after receiving the diagnosis of probable AD.

There were relatives and caregivers who stated that the elderly individuals never used BZD (55), while 16 did not know the history of use. Seventy-one elderly people (49.6%) stated that they had made use of BZD at some time during their lives. Twenty elderly patients had used it before receiving the diagnosis of AD and 19 started to use it after receiving this diagnosis: thus, 39 elderly people were using BZD. The BZDs that these individuals had used most during their lives were clonazepam, bromazepam, diazepam and flunitrazepam (long half-life). The length of use of BZDs ranged from one day to 50 years.

Therefore, it was possible to delineate a timeline for the use of benzodiazepines at some point in life, in relation to the diagnosis of probable Alzheimer's disease, among these elderly people. It was observed that the numbers of elderly patients taking BZD before (36) and after (35) receiving the diagnosis of AD were similar (**Figure 2**).

Only 9.1% and 1.4% of the elderly patients declared that they were alcohol users and smokers, respectively. However, 24 elderly people were former alcohol users and 49 former smokers.

After multivariate logistic regression, the severity of AD was found not to be a risk factor for the presence of the following drug risk variables: PIM use (P-value: 0.6838), occurrence of PII (P-value: 0.6838), use of polypharmacy (P-value: 0.0781) and occurrence of high-complexity MRCI (P-value: 0.8419).

However, from another perspective, simple logistic regression to assess whether the other variables identified in this study were risk factors for AD severity (such as sociodemographic characteristics or comorbidities, among others) showed that polypharmacy was the only possible risk factor for severity (P-value: 0.0206).

In addition, although comorbidities were not associated with AD severity, it was found that dyslipidemia (P-value: 0.0110), diabetes (P-value: 0.0352), hypertension (P-value: 0.041) and metabolic syndrome (P-value: 0.0376) were associated as risk factors for the presence of at least one of the drug risk variables.

Furthermore, from analysis on all comorbidities according to their ICD-10 classifications, the classes of mental and behavioral disorders (P-value: 0.0109) and circulatory system diseases (P-value: 0.0010) were also found to be associated with the presence of drug risk variables.

DISCUSSION

Most of the elderly people with AD, in the present study, showed drug risks due to polypharmacy and because they had comorbidities of anxiety, high cholesterol, hypertension, diabetes and metabolic syndrome.

It was observed that the drug therapy for these elderly individuals with AD was of low or medium complexity. We did not find any studies in the literature that identified or discussed the MRCI among elderly people with AD. However, a recent study showed that cognitive impairment was associated with lower MRCI scores than those of other chronic diseases.[32]

The complexity of drug therapy varies according to the morbidity that elderly patients present.[32] There are correlations not only with the number of drugs in use, but also with other factors such as dosage form and dosage schedule.[24]

On the other hand, although the drug therapy was assessed as presenting low to medium complexity, most of the elderly patients were using five or more drugs. Moreover, simple logistic regression showed that polypharmacy was the only drug risk factor associated with AD severity. Although we are not aware of any studies that have identified an association between polypharmacy and AD severity, there have been some recent studies showing that polypharmacy is a risk factor for dementia.[33,34]

Other studies have also correlated polypharmacy with prescription of PIMs[1] and occurrence of PIIs.[3] Presence of these factors is associated with increased mortality among elderly people.[35,36]

In the present study, the most commonly used PIM drug classes with PIMs and PIIs were antipsychotics and BZDs. Both of these classes are commonly prescribed for management of behavioral and psychological symptoms of dementia (BPSD).[37,38]

Even though antipsychotics are frequently prescribed for treating BPSD, this is an off-label use of this drug class, according to the Food and Drug Administration, since these are standard drugs for treating schizophrenia.[39] Opinions regarding the risk/benefit relationship of this use are divergent. While some studies have shown that antipsychotics are efficacious for improvement of BPSD,[40] others have shown that their use is associated with a more pronounced cognitive and functional decline and a lack of improvement of BPSD.[41]

The BZD class has mainly been prescribed for management of insomnia and anxiety. In contrast, because sleep disorders are usually related to brain changes arising from AD itself, it is not

Table 3. Frequency of use of potentially inappropriate medications (PIMs) and occurrence of potentially inappropriate interactions (PIIs), according to the assessment instruments and rationale, among elderly people with a probable diagnosis of Alzheimer's disease (n = 143), Araraquara, 2017

	n (%)	Rationale	Assessment instrument
Potentially inappropriate medications (ATC)			
Antipsychotics	**64 (44.6)**		
Quetiapine (N05AH04)	33 (23.0)	Increased risk of stroke and greater rate of cognitive decline and mortality among individuals with dementia. Potential risk of falls and fractures.	Updated Beers criteria (2015)[27]
Risperidone (N05AX08)	28 (19.6)	Use of antipsychotics for behavioral problems and delirium among patients with dementia should be avoided.	Updated Beers criteria (2015)[27]
Pericyazine (N05AC01)	3 (2.0)	Potential risk of falls and fractures.	French consensus panel[29]
Benzodiazepines	**39 (27.3)***		
Short-to-medium half-life			
Lorazepam (N05BA06)	1 (0.7)	Elderly people have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents.	Updated Beers criteria (2003 and 2015)[26,27]
Alprazolam (N05BA12)	4 (2.8)	In general, independent of half-life, all benzodiazepines increase the risks of cognitive impairment, delirium, falls, fractures and worsening of respiratory failure.	Updated Beers criteria (2003 and 2015)[26,27]
Estazolam (N05CD04)	1 (0.7)		Updated Beers criteria (2015);[27] French consensus panel[29]
Long half-life			
Clonazepam (N03AE01)	18 (12.6)	The rationale for long half-life benzodiazepines is the same as for short and medium. However, this use may be appropriate for eye movement sleep disorders, benzodiazepine withdrawal, severe anxiety disorder and periprocedural anesthesia.	Updated Beers criteria (2015)[27]
Flunitrazepam (N05CD03)	9 (6.3)		French consensus panel[29]
Bromazepam (N05BA08)	4 (2.8)		French consensus panel[29]
Diazepam (N05BA01)	2 (1.4)		Updated Beers criteria (2003 and 2015)[26,27]
Nitrazepam (N05CD02)	2 (1.4)		French consensus panel[29]
Flurazepam (N05CD01)	1 (0.7)	This has an extremely long half-life in elderly patients, such that it promotes prolonged sedation.	Updated Beers criteria (2015)[27]
Z-drugs	**5 (3.5)**		
Zolpidem (N05CF02)	5 (3.5)	Nonbenzodiazepines should be avoided, due to possible adverse events and minimal efficacy in treating insomnia. In addition, use of zolpidem can increase emergency department visits and hospitalizations, and motor vehicle crashes; it leads to minimal improvement in sleep latency and duration.	Updated Beers criteria (2015)[27]
Antidepressants	**11 (7.7)**		
Mirtazapine (N06AX11)	3 (2.1)	These may exacerbate or cause syndromes of inappropriate antidiuretic hormone secretion or hyponatremia. Sodium levels need to be monitored closely when starting use or changing dosages in older adults. They are highly anticholinergic and sedative, and cause orthostatic hypotension.	Updated Beers criteria (2015)[27]
Amitriptyline (N06AA09)	2 (1.4)		Updated Beers criteria (2003 and 2015);[26,27] STOPP/START v.2;[28] French consensus panel[29]
Nortriptyline (N06AA10)	2 (1.4)		Updated Beers criteria (2015)[27]
Clomipramine (N06AA04)	1 (0.7)		Updated Beers criteria (2015)[27]
Paroxetine (N06AB05)	1 (0.7)		Updated Beers criteria (2015)[27]

Continue...

Table 3. Continuation

	n (%)	Rationale	Assessment instrument
Fluoxetine (N06AB03)	2 (1.4)	This drug carries a risk of producing excessive stimulation of the central nervous system, sleep disturbances and increased agitation. In addition, there are risks of ataxia, worsening of psychomotor function and syncope. It may exacerbate or cause syndromes of inappropriate secretion of antidiuretic hormone or hyponatremia.	Updated Beers criteria (2003)[26]
Antiepileptics	**3 (2.1)**		
Phenobarbital (N03AA02)	2 (1.4)	High rate of physical dependence and greater risk of overdose at low dosages.	Updated Beers criteria (2015)[27]
Oxcarbazepine (N03AF02)	1 (0.7)	May exacerbate or cause syndromes of inappropriate antidiuretic hormone secretion or hyponatremia; sodium levels need to be monitored closely when starting use or changing dosages in older adults.	Updated Beers criteria (2015)[27]
Proton pump inhibitors	**10 (8.0)**		
Omeprazole (A02BC01)	7 (4.9)	Risk of *Clostridium difficile* infection and bone loss and fractures.	Updated Beers criteria (2015)[27]
Pantoprazole (A02BC02)	3 (2.1)	Avoid scheduled use for > 8 weeks unless for high-risk patients (e.g. oral corticosteroids or chronic NSAID use) or for erosive esophagitis, Barrett's esophagitis, pathological hypersecretory condition or demonstrated need for maintenance treatment (e.g. due to failure of drug discontinuation trial or H2 blockers).	Updated Beers criteria (2015)[27]
Diuretics	**6 (4.2)**		
Spironolactone (C03DA01)	6 (4.2)	In elderly patients with a creatinine clearance of less than 30 ml/min, serum potassium levels may be increased.	Updated Beers criteria (2015)[27]
Antihypertensives	**12 (9.1)**		
Immediate-release nifedipine (C08CA05)	7 (4.9)	Potential for hypotension; risk of precipitating myocardial ischemia and constipation.	Updated Beers criteria (2003 and 2015);[26,27] French consensus panel[29]
Propranolol (C07AA05)	5 (3.5)	-	Straand criteria (1999)[31]
Doxazosin (C02CA04)	1 (0.7)	Increases risk of orthostatic hypotension or bradycardia.	Updated Beers criteria (2003 and 2015)[26,27]
Antihyperglycemic	**2 (1.4)**		
Glibenclamide (A10BB01)	2 (1.4)	All sulfonylureas in general should be avoided among the elderly, because they can cause prolonged hypoglycemia and inappropriate secretion of antidiuretic hormone.	Updated Beers criteria (2015);[27] STOPP/START v.2[28]
Anti-Parkinsonian	1 (0.7)		
Biperiden (N04AA02)	1 (0.7)	Inappropriate for elderly people with dementia and delirium because it may worsen the cognitive and delirium.	Updated Beers criteria (2015);[27]STOPP/START v.2;[28] French consensus panel[29]
Antimicrobial	1 (0.7)		
Nitrofurantoin (J01XE01)	1 (0.7)	Potential for renal impairment, pulmonary toxicity, hepatoxicity, peripheral neuropathy or allergic reactions, especially with long-term use. Bacterial resistance in cases of protracted use can be observed.	Updated Beers criteria (2003 and 2015);[26,27] French consensus panel[29]
Antiarrhythmics	1 (0.7)		
Amiodarone (C01BD01)	1 (0.7)	Can be associated with QT interval problems and risk of provoking torsades de pointes. Amiodarone is effective for maintaining sinus rhythm but has greater toxicity than other antiarrhythmics used in atrial fibrillation.	Updated Beers criteria (2003 and 2015)[26,27]
Total number of PIMs	**159**		
Total number of elderly individuals	**91 (636%)**		
Average number of PIMs/ elderly individual [SD]	**186 (0.92)**		
Potentially inappropriate interaction (PII)			
Morbidity – drug			
Use of antipsychotics for non-psychotic diagnosis and in dementia	61	The risk/benefit relationship cannot be justified. Use should be avoided, due to adverse events at the central nervous system level.	Updated Beers criteria (2015)[27]

Continue...

Table 3. Continuation

	n (%)	Rationale	Assessment instrument
Dementia versus use of benzodiazepines and benzodiazepine receptor agonists	41	Aggravation of cognitive impairment. Possible adverse drug events at central level.	Updated Beers criteria (2015);[27] French consensus panel[29]
Depression versus long-term use of benzodiazepines	32	May produce or exacerbated depression.	Updated Beers criteria (2003)[26]
Cognitive impairment versus use of tricyclic antidepressants	7	Risk of worsening cognitive impairment.	STOPP/START v.2[28]
Depression versus active metabolites of tricyclic antidepressants	7	May cause anticholinergic side effects.	Canada national consensus panel[30]
Absence of clinical history of coronary and cerebral symptoms and vascular peripheral occlusion; diabetes mellitus; arterial hypertension versus use of acetylsalicylic acid	4		STOPP/START v.2[28]
Dementia versus use of neuroleptics	3	Risk of worsening cognitive impairment.	French consensus panel[29]
Cognitive impairment versus use of barbiturates	2	Concern about effects on the central nervous system.	Updated Beers criteria (2003)[26]
Parkinson's disease versus use of all antipsychotics except quetiapine	2	Concern due to their antidopaminergic and cholinergic effects.	Updated Beers criteria (2003)[26,27]
Diabetes mellitus versus use of corticosteroids	1	May worsen diabetes mellitus; serum glucose levels need to be monitored.	Canada national consensus panel[30]
Drug - drug			
≥ 3 CNS-active drugs** in use	17	Increased risk of falls and fractures.	Updated Beers criteria (2015)[27]
Total number of PIIs	**177**		
Total number of elderly individuals	**91 (63.6%)**		
Average number of PIIs/ elderly individual [SD]	**2 [1.42]**		

n = number of elderly; SD = standard deviation; ATC = Anatomical Therapeutic Chemical.
*An elderly person can make use of more than one BZD simultaneously; **CNS (central nervous system)-active drugs: antipsychotics, benzodiazepines, nonbenzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors and opioids.

clear whether the drugs actually used are effective, since the use of these drugs in the context of comorbid neurological disease is also considered to be off-label.[42,43]

With regard to chronic use of BZD as a risk factor for AD, a recent meta-analysis showed that its use was a risk factor.[44] From another perspective, a systematic review identified studies in which negative effects from BZD on the cognition of elderly people who already had the diagnosis of AD were reported.[45]

However, we did not find any association between use of BZD and cognitive impairment or progression of AD. This may be explained by the chronic use of BZD before and after the diagnosis of AD was made, the absence of the clinical parameters of MMSE and CDR and the small sample size.

In addition, it was observed that MetS and its risk factors (cholesterol, hypertension and diabetes) and anxiety (a comorbidity that is considered to be a prodromal symptom of AD) were associated with drug risk.

MetS was previously shown to be a risk factor for AD.[46,47] Its presence allowed the trajectory of the prodromal stage of AD to become significantly extended to the symptomatic stage.[46] BPSD have been found to be present both before the diagnosis and during the course of the disease.[37]

Anxiety was an aggravating factor for drug safety among the elderly individuals with AD in the present study and was usually treated with BZD. MetS risk factors were treated with immediate-release nifedipine, propranolol and glibenclamide, and all of these were considered to be PIMs. Nevertheless, these PIMs have been standardized as essential by the WHO and by RENAME-Brazil. However, their respective safer therapeutic equivalents for the elderly, i.e. captopril, losartan and metformin, have also been standardized.

Another important finding from the present study was the absence of determinations of clinical MMSE and CDR parameters among the patients. These findings show that no monitoring of the effectiveness of this drug therapy was being done and, consequently, that there was non-compliance with the guidelines recommended in the PCDTDA/MS.[48] Therefore, the "minor" complexity of the drug therapy for these elderly individuals with AD did not mean that there were no safety issues or drug-related problems (DRPs) to be identified, prevented, monitored and resolved.

In this context, medication therapy management based on the underlying disease, taking into account the comorbidities and therapeutic experience of the patient and family/caregiver, may be form of pharmaceutical care that would be of interest for promoting drug safety, compliance with drug therapy[49] and resolution of DRPs.[50,51]

Thus, important data about the drug safety of patients with Alzheimer's disease were identified through the present study. Our findings suggest that patients with AD should be regarded in an overall manner: not only managing the number of drugs in

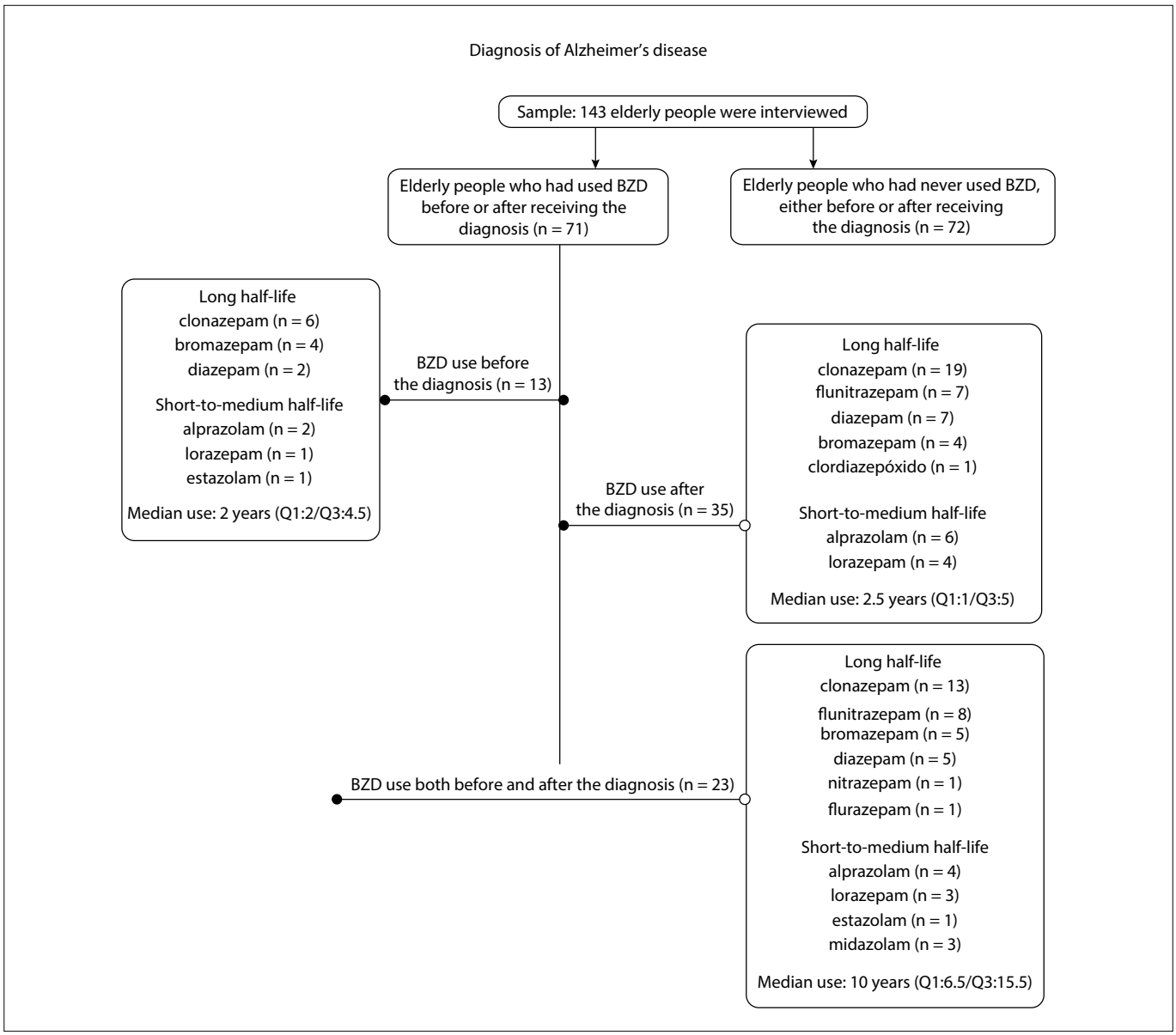

Figure 2. Description of the use of benzodiazepines (BZD) during the patients' lives, in relation to their diagnoses of Alzheimer's disease (n = 143), Araraquara, 2017.

use or the complexity of drug therapy, but also taking into account the patient's needs and comorbidities, along with the experience and expectations of the caregiver/familiar regarding the treatment, and the outcomes when drug risk variables are present.

Limitations of this study

The main limitation of this study was that the severity of AD was assessed through insertion of memantine, because of absence of the clinical parameters of MMSE and CDR. These clinical parameters are considered to be the gold standard and should be ascertained every six months, as recommended by PCDTDA/MS.

Another limitation was the losses of the present study. However, inclusion in this study of incomplete data obtained through interviews with family members/caregivers who were unaware of the clinical history of the elderly patients would have constituted a form of bias. Nonetheless, this inclusion would have diminished the limitations.

Moreover, the cross-sectional design of this study did not allow us to identify causal associations.

CONCLUSION

Even though the drug therapy of our elderly patients with AD was of low complexity, the majority of these drugs presented safety risks in relation to the comorbidities of anxiety, cholesterol, hypertension, diabetes and metabolic syndrome. Although we did not identify any evidence in the literature that would correlate polypharmacy with AD severity, our data suggest that this is a possible drug safety risk. Off-label use of PIMs, such as risperidone, quetiapine and benzodiazepines like clonazepam and flunitrazepam, also present a drug safety risk for elderly people with AD.

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Inadequacies of musculoskeletal medicine curriculum for undergraduate medical students: a cross-sectional study

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ABSTRACT

BACKGROUND: Musculoskeletal disorders account for up to one in four of general-practice consultations and almost one third of complaints in primary-care clinical practice. However, an insufficient amount of time and importance is given to their teaching in most medical schools.

OBJECTIVE: To evaluate the acquisition of musculoskeletal competences in our institution, in order to identify flaws and propose changes to correct and improve the musculoskeletal curriculum.

DESIGN AND SETTING: Cross-sectional study conducted in São Paulo, Brazil.

METHODS: First to fifth-year medical students were enrolled in a survey using the Freedman and Bernstein musculoskeletal examination, in order to evaluate the acquisition of musculoskeletal competencies. Categorical data were analyzed using the chi-square test. Continuous data were analyzed using one-way analysis of variance (ANOVA). The level of significance was set as $P < 0.05$.

RESULTS: A total of 545 students completed the questionnaire: from year 2, 115/167 (29.6%); from year 3, 118/138 (30.4%); from year 4, 98/130 (25.3%); and from year 5, 57/110 (14.7%). None of the students achieved the pass mark (established as 70%). The level of confidence in performing musculoskeletal examination was very low (3.7 ± 2.2; $n = 386$) and bore no relationship to the percentage of correct answers in the questionnaire ($r = 0.331$; 95% confidence interval, CI: 0.239-0.417; $P < 0.001$).

CONCLUSION: Undergraduate teaching is the only exposure most general practitioners have to orthopedic problems. Universities are concerned about the adequacy of the musculoskeletal programs taught in their institutions. Student scores were found to be unsatisfactory in all the topics evaluated.

INTRODUCTION

Musculoskeletal disorders account for up one in four general-practice consultations[1] and almost one third of complaints in primary-care clinical practice. However, an insufficient amount of time and importance is given to their teaching in most medical schools.[2,3] Moreover, the knowledge acquired is not always in line with what professors desire or plan. Active techniques have been included in undergraduate training as a powerful teaching tool for improving the quality of learning.

Knowledge of the basis of musculoskeletal disorders is fundamental for general practitioners, family practitioners, pediatricians, emergency physicians, interns and, of course, rheumatologists and orthopedists. Thus, a very well-structured curriculum is necessary in order to achieve the competences desired.

One way to evaluate the basic competency attained by medical school students in relation to the musculoskeletal system is the Freedman and Bernstein examination. This was developed and validated by 124 chairs of orthopedic residency programs in the United States and the pass mark for physicians has been set at 70%.[4]

OBJECTIVE

The objective of this study was to evaluate the acquisition of musculoskeletal competences in our institution, in order to identify flaws and propose changes to correct and improve the musculoskeletal curriculum.

METHODS

Aspects of the musculoskeletal system are taught a little at a time each year up to the end of the fourth year in our medical school. Thus, second to fifth-year medical school students were

enrolled in a survey in which they were asked to complete the Freedman and Bernstein musculoskeletal examination[4] and to fill in a form containing questions regarding demographic information, including their year of training, personal preferences among subspecialties in medicine (clinical area of interest) and feelings about the time spent on theoretical and practical classes during the whole period of musculoskeletal training that they had had up to that moment.

To assess the students' perceptions regarding their classes, a five-point bipolar measurement scale (five categories) centered on "indifferent" was used. The five categories were: far too many classes (the number could be reduced); good number of classes (not too many and not too few); reasonable number of classes (enough, but more classes would be welcome); insufficient number of classes (more classes definitely needed); very poor number of classes (not enough time dedicated to classes)

The types of active teaching methodologies that the students had had over the course of their undergraduate studies up to that point, and the percentage of each type, were assessed.

A tool asking about their confidence in performing orthopedic physical examinations and making diagnostic hypotheses for musculoskeletal disorders was applied using a 10-point scale. The confidence scores was grouped as 0-3 (low), 4-7 (moderate) and 8-10 (high).

The testing was performed with the cooperation of the professors of each year. Written informed consent was obtained from the participants and the examination was anonymous. No time limit was imposed.

The distribution of academic content, according to the semester taught, is shown in **Table 1**. Anatomy content is taught by the end of the second year, while major clinical and therapeutic content is taught by the end of the fourth year.

The general characteristics of the sample are shown in **Table 2**. In total, 388 (71.2%) out of 545 students completed the questionnaires. The split according to year was as follows: year 2 = 115/167 (29.6%); year 3 = 118/138 (30.4%); year 4 = 98/130 (25.3%); and year 5 = 57/110 (14.7%).

The Freedman and Bernstein examination was developed and validated to test how well medical school graduates understood basic musculoskeletal problems.[4] The questionnaire consists of 25 short open questions about important topics such as fractures, tumors, dislocations, back pain, arthritis and emergencies that need

Table 1. Contents of the Freedman and Bernstein musculoskeletal questionnaire according to the semester taught and curricular unit

Question	Semester (curricular unit) / Topic	1	2	3	4	5	6	7	8
1	Congenital dislocation of the hip					MPV		OT	
2	Compartment syndrome	Mo		LS			GS	OT	
3	Arthritis (septic or inflammatory)				MPIV			OT	
4	Knee displacement			LS				OT	
5	Open fracture							OT	
6	Low back pain (differential diagnosis: tumor/infection)				MPIV			OT	
7	Compartment syndrome	Mo					GS	OT	
8	Upper limb fractures (scaphoid)			LS				OT	
9	Hip dislocation							OT	
10	Carpal tunnel syndrome (clinical and anatomical)			LS	MPIV			OT	Ne
11	Disc herniation; orthopedic and neurological propaedeutics				MPIV			OT	
12	Anatomy of peripheral nerves				NS			OT	
13	Fractures and ligament sprain in children							OT	
14	Low back pain				MPIV		AH	Rh	
15	Anatomy of peripheral nerves in lower limbs				NS				
16	Knee effusion and hemarthrosis							OT	
17	Bone tumor							OT	
18	Rheumatoid arthritis and osteoarthrosis							Rh	
19	Bone tumor or myeloma							OT	
20	Anatomy of knee ligaments			LS				OT	
21	Osteoporosis and/or osteomalacia				MPIV	MPV	AH	Rh	
22	Proximal femur fracture and/or hip vascular anatomy			LS				OT	
23	Anatomy of upper limb muscles and/or lateral epicondylitis			LS				OT	
24	Anatomy of upper limb muscles			LS					
25	Anatomy of upper limb muscles and/or rotator cuff			LS				OT	

Mo = morphology; LS = locomotor system; NS = nervous system; MPIV = medical practices IV; MPV = medical practices V; GS = general surgery and anesthesiology; AH = adult health; OT = orthopedics and traumatology; Rh = rheumatology; Ne = neurology.

to be recognized by general physicians so that patients with these conditions can be referred to an orthopedic surgeon immediately.

The examination was scored anonymously using an answer key. The pass mark was set as 70%, based on recommendations from previous studies.[4,5] Each question was worth a maximum of one point and the raw scores were multiplied by four to obtain a final score between zero and 100.

The lesson plans of the previous year were evaluated and used as a reference to determine whether the topic had been taught to the students and in which year of the medical curriculum this had been done.

The results were analyzed using the R software (version 3.3.2, 2016; Vienna, Austria) and graphs were compiled using the ggplot2 package. Descriptive data and confidence intervals were determined. Categorical data were analyzed using the chi-square test. Continuous data were analyzed using one-way analysis of variance (ANOVA). The significance level was set as $P < 0.05$.

RESULTS

None of the students achieved the pass mark, which had been established as 70%. There was no difference in the percentage of correct answers between the third-year students (16.2 ± 9) and the fifth-year students (16.3 ± 14.4). The students' overall performance was very low (**Figure 1**).

Out of all the questions, the first question (What common problem must all newborns be examined for?) received the most correct responses (49.7% ± 50.1), while question 11 (A patient had a disc herniation pressing on the fifth lumbar nerve root. How is motor function of the fifth lumbar nerve root tested?) received the fewest correct responses (0.5% ± 7.7).

Based on the hypothesis that students starting out in medical school would perform better in relation to questions of basic anatomy while students in the later years would score better in relation to important clinical questions, a group component score was obtained by forming the following groups: anatomy-based questions (numbers 8, 10, 11, 12, 15, 20, 22, 23, 24 and 25); "red-flag" questions (numbers 2, 4, 5, 6 and 7); and miscellaneous questions (numbers 1, 3, 9, 13, 14, 16, 17,18, 19 and 21). Red-flag questions related to situations that are considered to be clinical emergencies, in which non-recognition can cause irreparable harm to the patient. They were answered most successfully by the fifth-year students (**Figure 2**), albeit with a low incidence of correct answers. On the other hand, basic anatomy questions were answered most successfully by the third-year students, and the percentage of correct answers decreased over the subsequent years (**Figure 3**).

Excluding second-year students, no difference in the proportion of correct answers was found in relation to the miscellaneous questions among the other school years (**Figure 4**).

The level of confidence in performing musculoskeletal examination was very low (3.7 ± 2.2; n = 386) and bore no relationship to the percentage of correct answers in the questionnaire (r = 0.331; 95% confidence interval, CI: 0.239-0.417; $P < 0.001$). The level of confidence in performing physical examination was highest in the third year (4.8 ± 1.7; n = 118).

The students' perceptions of the teaching methods used by professors and the amounts of time spent on theoretical and practical

Table 2. General characteristics of the sample

	Year 2	Year 3	Year 4	Year 5
Number of students	115	118	98	57
Gender				
Male	27	32	35	19
Female	88	86	63	38
Mean age (years)	21.3	22.8	23.6	25.1

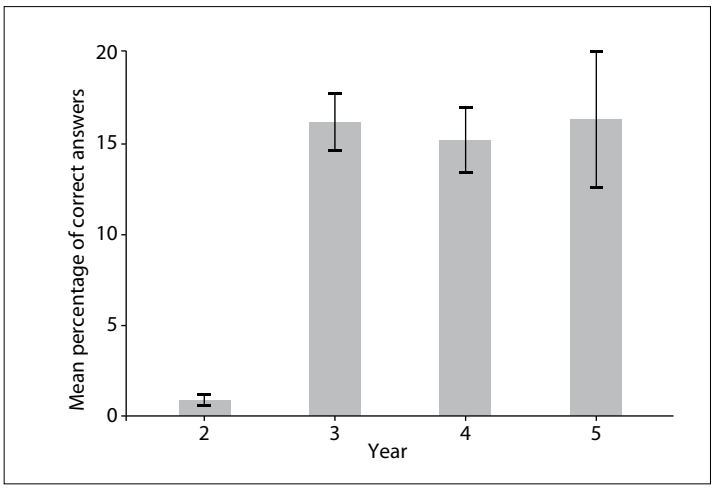

Figure 1. Distribution of correct answers for each school year. Results expressed as mean percentage and 95% confidence interval.

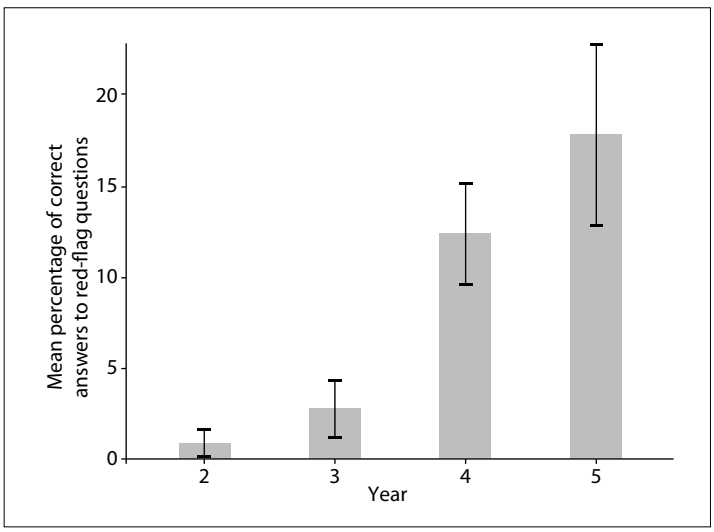

Figure 2. Distribution of correct answers to red-flag questions according to school year. Data expressed as mean and 95% confidence interval.

classes are shown in **Table 3**. The majority (83.7%) of the students considered that the amount of time spent on theoretical classes was reasonable or good (83.7%). Theoretical classes were the most commonly used teaching methodology (44.5% ± 23.4; n = 349).

DISCUSSION

In this study, we evaluated students in the second to the fifth academic years of medical school using a survey based on the Freedman and Bernstein questionnaire, to analyze their progress in achieving musculoskeletal competencies. None of the students attained the pass mark of 70%. Fifth-year students performed better on red flag questions while third-year students performed better on anatomy questions. The students' level of confidence in performing musculoskeletal examinations was very low (< 5, on a scale of 0-10 points).

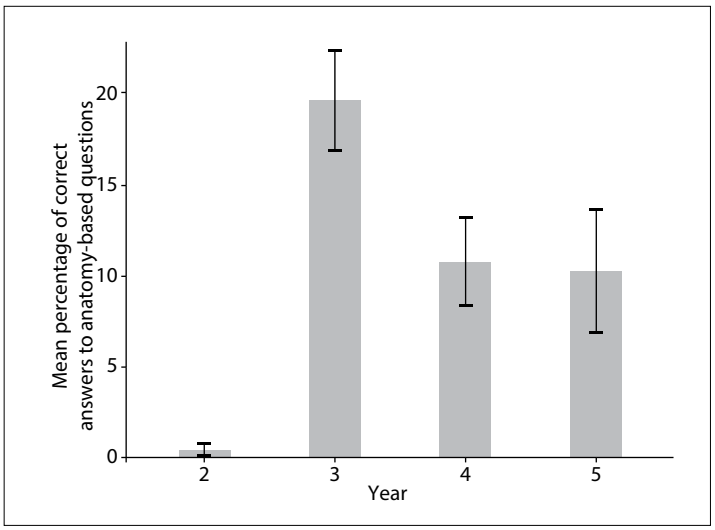

Figure 3. Distribution of correct answers to basic anatomy questions according to school year. Data expressed as mean and 95% confidence interval.

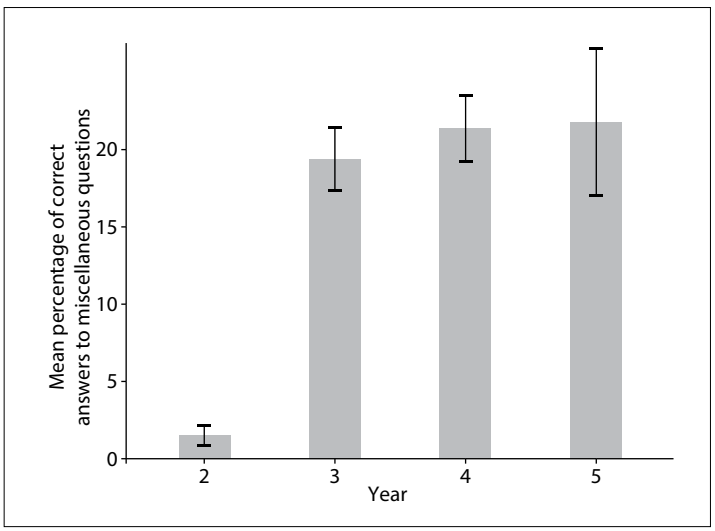

Figure 4. Distribution of correct answers to miscellaneous questions according to school year. Data expressed as mean and 95% confidence interval.

The burden of musculoskeletal problems within primary-care medical practice and on healthcare resources is well known.[6-8] However, undergraduate teaching is the only exposure that the majority of general practitioners will have to orthopedic problems. Many universities are concerned about the adequacy of the musculoskeletal programs taught in their institutions.[1,4,5,7–11] The present study serves to aid in understanding and proposing changes since our students correctly answered fewer than 20% of the questions.

However, it is important to look not only at the curriculum but also, and sometimes even more importantly, at the way in which the curricular content is being taught. At our institution, we use the spiral curricular model, in which students see content more than once (**Table 2**). However, although active methodologies are used, students are not retaining that knowledge.

Third-year students performed better on basic or anatomical questions, which they had just finished studying through the spiral curriculum, but the level of correct responses decreased over the subsequent years. This may have been due to many factors, such as the methodologies used or differences in the way in which the content was taught, since some changes to the teaching staff occurred during this period.

Fifth-year students performed better in the so-called red-flag set of questions. This was because the major clinical and therapeutic content had been taught that year. Unfortunately, students in the sixth year were not evaluated in this study: this would have enabled analysis on the students' learning.

Attention needs to be given to curricular competencies. In Brazil, competencies have been well described in relation to the medical curriculum but not for curricular subjects.[12] Thus, there is no standardization regarding the musculoskeletal curriculum for all universities and each professor or institution can decide what is important to teach, and sometimes they do not cover all the core subjects. There is also the possibility that professors are not fulfilling the lesson plan. Since this study was conducted in only one institution, we are unable to say whether this is the case throughout the country, but our study sheds light on an area that deserves attention.

CONCLUSION

In summary, the way in which musculoskeletal disorders are being taught in medical schools today needs to be reviewed. There is scope for progress in relation to some points, such as the standardization of content, commitment of teachers to teaching this content, improvement of active teaching methodologies, use of sound in-depth lesson plans and supervision and confirmation that these plans are being fulfilled.

Table 3. Students' perceptions of the types of class per school year

Class mode		Year					P-value
		2 (n = 115)	3 (n = 118)	4 (n = 98)	5 (n = 57)	Total (n = 388)	
Theoretical class time	Very poor number of classes	4 (3.5%)	8 (6.8%)	13 (13.3%)	14 (25.5%)	39 (10.1%)	< 0.001
	Insufficient number of classes	4 (3.5%)	1 (0.8%)	4 (4.1%)	6 (10.9%)	15 (3.9%)	
	Reasonable number of classes	59 (51.3%)	52 (44.1%)	49 (50%)	19 (34.5%)	179 (46.4%)	
	Good number of classes	46 (40%)	56 (47.5%)	30 (30.6%)	12 (21.8%)	144 (37.3%)	
	Far too many classes	2 (1.7%)	1 (0.8%)	2 (2%)	4 (7.3%)	9 (2.3%)	
Practical class time	Very poor number of classes	18 (15.8%)	12 (10.2%)	25 (25.5%)	15 (27.3%)	70 (18.2%)	< 0.001
	Insufficient number of classes	7 (6.1%)	4 (3.4%)	12 (12.2%)	17 (30.9%)	40 (10.4%)	
	Reasonable number of classes	52 (45.6%)	48 (40.7%)	43 (43.9%)	16 (29.1%)	159 (41.3%)	
	Good number of classes	37 (32.5%)	52 (44.1%)	13 (13.3%)	6 (10.9%)	108 (28.1%)	
	Far too many classes	0 (0%)	2 (1.7%)	5 (5.1%)	1 (1.8%)	8 (2.1%)	
TBL (mean ± SD)		20.2 ± 25.9 (n = 104)	13.5 ± 12.3 (n = 115)	9.4 ± 12.5 (n = 91)	17.9 ± 14 (n = 40)	14.9 ± 18.1 (n = 350)	< 0.001
PBL (mean ± SD)		10.7 ± 19.6 (n = 103)	6 ± 9.8 (n = 115)	5.8 ± 14.3 (n = 91)	14.2 ± 17.6 (n = 40)	8.3 ± 15.5 (n = 349)	0.004
Case study (mean ± SD)		21.6 ± 23.2 (n = 104)	11.9 ± 12.4 (n = 114)	9.1 ± 12.3 (n = 90)	11 ± 13 (n = 40)	14 ± 17.2 (n = 348)	< 0.001
Dialogued lecture class (mean ± SD)		48.1 ± 24.9 (n = 104)	38.9 ± 21.4 (n = 115)	40.4 ± 20.5 (n = 91)	61.5 ± 22 (n = 39)	44.5 ± 23.4 (n = 349)	< 0.001
Laboratory classes (mean ± SD)		36 ± 27.2 (n = 104)	26.9 ± 18.5 (n = 115)	24.2 ± 18.7 (n = 91)	17.9 ± 18.7 (n = 39)	27.9 ± 22.2 (n = 349)	< 0.001
Practice with patients (mean ± SD)		17.3 ± 24.6 (n = 104)	16.2 ± 15.2 (n = 115)	16.6 ± 16.8 (n = 90)	15.2 ± 13.1 (n = 39)	16.5 ± 18.6 (n = 348)	0.935
Body painting (mean ± SD)		9.3 ± 13.2 (n = 104)	5.2 ± 6.4 (n = 114)	7.5 ± 11.8 (n = 90)	8.4 ± 10.7 (n = 39)	7.4 ± 10.8 (n = 347)	0.038
Peer-to-peer (mean ± SD)		10 ± 17.6 (n = 103)	6.1 ± 9.8 (n = 115)	5.9 ± 7.4 (n = 91)	8.4 ± 12.8 (n = 39)	7,5 ± 12.6 (n = 348)	0.066
Others (mean ± SD)		0.1 ± 0.7 (n = 104)	0.1 ± 1.1 (n = 115)	1.2 ± 4.3 (n = 91)	0.5 ± 2.2 (n = 39)	0.4 ± 2.5 (n = 349)	0.008

TBL = team-based learning; PBL = problem-based learning; SD = standard deviation.

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Free access to medicines among older adults in primary care: a cross-sectional study

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Public health.
Pharmaceutical preparations.
Pharmaceutical services.

AUTHORS' KEY WORDS:
Elderly.
Medicines.
Access to medicine.

ABSTRACT

BACKGROUND: Access to medicines is an important indicator of healthcare system quality and capacity to resolve problems. The healthcare system needs to ensure free access to medicines for elderly people, in order to provide greater effectiveness of disease control, thus reducing morbidity and mortality, and improving health and quality of life.

OBJECTIVES: To analyze the frequency of free access to medication among older adults within primary care and determine the factors associated with free access.

DESIGN AND SETTING: Cross-sectional study at two primary care units.

METHODS: Free access was defined as provision of all medicines through pharmacies within the Brazilian National Health System and through the Brazilian program for free medicines in private pharmacies. We investigated the sociodemographic, clinical, functional and pharmacotherapeutic characteristics of older adults. Multivariate logistic regression was performed to identify factors associated with free access to medicines.

RESULTS: This study included 227 older adults, among whom 91 (40.1%) had free full access to prescription drugs. A direct association with age ≤ 70 years and indirect associations with polypharmacy and multimorbidity ($P < 0.05$) were found.

CONCLUSIONS: Age ≤ 70 years increases the likelihood of having free full access to medicines, and older adults with multimorbidity and polypharmacy use have a lower likelihood of access. Identification of factors associated with free access to medicines among elderly people provides elements to guide the Brazilian National Health System in implementing access improvement actions.

INTRODUCTION

The contribution of medicines to better quality of life, recovery of health and increased survival is appreciable.[1] Thus, resolute public healthcare actions to curb morbidity and mortality are strongly influenced by rational access to and use of drugs.[1-4]

Given the increasing burden of chronic noncommunicable diseases around the world, access to medicines encompassing availability and affordability is a significant public health challenge for both developed and developing countries. The global action plan for noncommunicable disease prevention and control coordinated by the World Health Organization recommends that actions to expand access to medicines should be developed.[5,6]

In Brazil, through the National Drug Policy, measures have been implemented to ensure and expand the population's access to medicines since 1998. In 2004, actions were scaled up when the National Pharmaceutical Services Policy Guidelines were defined.[4,7] The following stand out among the different strategies for improving access to medicines that are underway in this country: structuring of pharmaceutical services; improvement and innovation of the legal framework for accessing medicines within the Brazilian National Health System; improved organization of financing for public pharmaceutical services; and higher levels of federal resources for procurement of medicines.[4]

Brazil has been experiencing aging of the population as a result of the epidemiological and demographic transition that is taking place in this country. This situation greatly affects the planning of social and healthcare policies, given the increased prevalence of older adults with multiple noncommunicable diseases requiring complex multidrug therapy.[1,8,9] The National Survey on Drug Access, Use and Promotion of Rational Use in Brazil found that 75.7% of older adults used

two or more chronic drugs.[1] Given this scenario, healthcare systems need to ensure free access to medicines for elderly people, in order to provide greater effectiveness of disease control, thus reducing morbidity and mortality, and improving health and quality of life.[3-6]

Access to medicines is an important indicator of healthcare system quality and capacity to resolve problems and is considered by the United Nations to be an appropriate means for measuring progress towards achievement of healthcare rights.[7,10-13]

Primary healthcare is provided through an extensive network of services and can solve most of a population's health problems. Consequently, ensuring free access to medicines for older adults at this level of care should be a priority.[7,9]

OBJECTIVE

The aims of this study were to analyze the frequency of free access to medication among elderly people attended at two primary healthcare centers and to determine the factors associated with free access.

METHODS

Study design and participants

This was a cross-sectional study conducted at two primary care units (PCUs) located in the city of Belo Horizonte, Brazil. The study population consisted of individuals aged 60 years and over (older adults) who received at least one drug from PCU pharmacies between November 2013 and April 2014. The participants were selected non-randomly, and older adults were invited consecutively to participate in the study in PCU pharmacies. The exclusion criterion was the inability to communicate verbally or visually.

Sample

The sample size was calculated from data in the computerized pharmacy system of the PCU. The mean monthly number of visits to these pharmacies by elderly people was 483. Based on the premise that dispensing of chronic care drugs from PCU pharmacies is done monthly, we considered that elderly people who were attended every month were part of the same population. Thus, by assuming that there was a finite population of 483 older adults, with a prevalence value of 50% for all observed characteristics, and taking a significance level of 5%, confidence interval of 95% and loss or refusal rate of 10%, the sample size was estimated to be 237 older adults. The "Open Epi" version 3.01 software was used for the sample size calculation.[14]

Data collection and organization

Data were collected through face-to-face interviews, using a structured questionnaire that was applied by pharmacists and by pharmacy and medical students who had previously received training. The questions were on sociodemographic, clinical, functional, access-related and medicine-use characteristics. These data were complemented by consulting the medical records. The information on access to medicines covered the period of the last 30 days. The database was created using the Epi Info version 3.5.4 software (Centers for Disease Control and Prevention, Atlanta, United States). Quality control relating to data entry was performed by replicating 10% of the interviews. Reliability analysis among the data input typists was performed through kappa statistics, which showed a mean value of 1.0, thus indicating ideal agreement. These analyses were performed using the Statistical Package for the Social Sciences 25.0 software (SPSS 25.0).

Variables

The dependent variable was full free access within the Brazilian National Health System to the drugs prescribed in the last 30 days. Free access included access to all prescription drugs. The category of free access included medicines received at PCUs and other services of the Municipal Health Department of Belo Horizonte, at specialized component pharmacies and through the *Saúde Não Tem Preço* (Health Doesn't Have A Price) program at private pharmacies. Specialized component pharmacies are public utilities that provide medicines for specialized care. Under the *Saúde Não Tem Preço* program, users obtain drugs from private pharmacies without co-payment fees, with costs funded by the Ministry of Health.

The numbers of drugs obtained from public-system pharmacies and private pharmacies were ascertained established. The drugs included in the municipal essential medicines list (MEML) of Belo Horizonte were identified and then classified in accordance with level one of the World Health Organization's Anatomical Therapeutic Chemical (ATC) system. The independent variables were divided as follows: (i) **sociodemographic**: gender, age, education, skin color, income and marital status (reclassified as with or without a partner); (ii) **clinical characteristics**: multimorbidity (≥ 2 diseases),[15] classification of self-reported comorbidities, depressive symptoms and self-perceived health; (iii) **functional characteristics**: cognition, basic activities of daily living (BADL) and instrumental activities of daily living (IADL); and (iv) **pharmacotherapeutic**: polypharmacy (use of five or more prescription drugs).

Scales that had been validated or adapted for the Brazilian context were used to evaluate the following variables: **depression** – 15-item Geriatric Depression Scale (individuals with depressive symptoms: ≥ 6 points);[16] **cognition** – Mini-Mental State Examination (individuals with cognitive disability were defined as those presenting ≤ 13 points if they were illiterate; ≤ 18 points if they had had one to eight years of schooling; and ≤ 24 points if they had had more than eight years of schooling);[17,18] **basic activities of daily living** – Katz scale;[19] and **instrumental activities of**

daily living – Lawton and Brody scale (independent individuals = 21 points).[20]

Self-perceived health was measured by asking the patient: "In general, compared with other people of your age, would you say that your health is excellent, very good, good, fair or poor?" A positive assessment would comprise the responses "excellent", "very good" or "good", whereas a negative assessment would include the other answers, namely, "fair" or "poor".

Statistical analysis

Descriptive analysis was performed by determining the relative and absolute frequencies of categorical variables, and the median, interquartile range (IQR), minimum (min) and maximum (max) of quantitative variables. The association between free full access to prescription drugs within the Brazilian National Health System and the independent variables was analyzed using Pearson's chi-square test. Continuous variables were dichotomized based on medians or definitions in the literature.

Variables with $P \leq 0.20$ in univariate analyses were included in a multivariate logistic regression, and those with $P \leq 0.05$ were retained in the final model. The goodness-of-fit of the final model was evaluated using the Hosmer-Lemeshow test (good fit if $P > 0.05$). Data analysis was performed using the SPSS 25.0 software.

Ethical issues

The research project was approved by the research ethics committees of a public university and of the Municipal Health Department of Belo Horizonte on August 8, 2013, through protocol number CAAE 17339713.40000.5149. The older adults who agreed to participate signed an informed consent statement.

RESULTS

The characteristics of the 227 elderly people who participated in the study are shown in **Table 1**. Their median age was 70 years (IQR = 12; minimum = 60 and maximum = 93); most were female (70.9%) and the majority had monthly income below two minimum wages (60.9%). These older adults predominantly presented preserved cognition (86.1%), independence in relation to BADL (76.5%) and partial independence in relation to IADL (77.1%). None of these elderly people were classified as totally dependent in relation to performing BADL or IADL.

Regarding clinical characteristics, the median number of self-reported diseases was three (IQR = 2), and 92.1% had multimorbidity. The most frequent diseases reported by these elderly people were hypertension (86.3%), musculoskeletal diseases (34.4%) and diabetes (32.6%). A positive self-perception of health was reported by 69.9% of the participants.

Regarding pharmacotherapeutic characteristics, the median number of medications used by these elderly people was five

Table 1. Description of older adults attended at the two healthcare centers (n = 227)

Variables	Free-access medicines		General description
	Yes	No	
	n (%)	n (%)	n (%)
Sociodemographic factors			
Gender			
Female	57 (35.4)	104 (64.6)	161 (70.9)
Male	34 (51.5)	32 (48.5)	66 (29.1)
Age			
≤ 70 years	53 (46.5)	61 (53.5)	114 (50.2)
> 70 years	38 (33.6)	75 (66.4)	113 (49.8)
Skin color			
Black	20 (45.5)	24 (54.5)	44 (19.5)
Other	70 (38.5)	112 (61.5)	182 (80.5)
Schooling			
> 4 years	41 (37.3)	69 (62.7)	110 (48.7)
≤ 4 years	49 (42.2)	67 (57.8)	116 (51.3)
Married			
Yes	42 (48.8)	44 (51.2)	86 (38.4)
No	48 (34.8)	90 (65.2)	138 (61.6)
Income			
> 2 minimum monthly wages	34 (40.5)	50 (59.5)	84 (39.1)
≤ 2 minimum monthly wages	51 (38.9)	80 (61.1)	131 (60.9)
Functional factors			
Cognition			
Preserved	79 (41.1)	113 (58.9)	192 (86.1)
Suspected disability	12 (38.7)	19 (61.3)	31 (13.9)
Instrumental activities of daily living			
Independent	25 (48.1)	27 (51.9)	52 (22.9)
Partially dependent	66 (40.1)	136 (59.9)	175 (77.1)
Basic activities of daily living			
Independent	73 (42.2)	100 (57.8)	173 (76.5)
Dependent ≥ one activity	18 (34.0)	35 (66.0)	53 (23.5)
Clinical factors			
Multimorbidity			
Yes	78 (37.3)	131 (62.7)	209 (92.1)
No	13 (72.2)	5 (27.8)	18 (7.9)
Arterial hypertension			
Yes	79 (40.3)	117 (59.7)	196 (86.3)
No	12 (38.7)	19 (61.3)	31 (13.7)
Diabetes mellitus			
Yes	24 (32.4)	50 (67.6)	74 (32.6)
No	67 (43.8)	86 (56.2)	153 (67.4)
Asthma and chronic obstructive pulmonary disease			
Yes	10 (29.4)	24 (70.6)	34 (15.0)
No	81 (42.0)	112 (58)	193 (85.0)
Depressive symptoms			
Yes	17 (34.0)	33 (66.0)	50 (22.5)
No	74 (43.0)	98 (57.0)	172 (77.5)
Self-perceived health			
Positive	63 (39.9)	95 (60.1)	158 (69.9)
Negative	28 (41.2)	40 (58.8)	68 (30.1)
Pharmacotherapeutic factors			
Polypharmacy			
Yes	44 (33.1)	89 (66.9)	133 (58.6)
No	47 (50.0)	47 (50.0)	94 (41.4)

(IQR = 3; minimum = 1 and maximum = 13), and 58.6% were using polypharmacy.

Figure 1 shows the characterization of access to medicines among these 227 older adults. Among them, 67 (29.5%) reported having full access to all medicines at the PCU pharmacies investigated. Access to at least one drug in the PCU pharmacies surveyed was reported by 32 (14.1%) of these older adults. We found that 128 (56.4%) of these elderly people had bought or received at least one drug through a channel other than the PCU.

The analysis on medicines that were not accessed at PCU pharmacies showed that the access strategies most used by the elderly people were the following: acquisition at a private pharmacy with the total amount paid by the user (41.9%); free access through the *Saúde Não Tem Preço* program (25.0%); and access through the popular pharmacy program, with acquisition subsidized by the Ministry of Health with co-payment fees (23.4%), as shown in **Figure 1**. Full access to the prescribed drugs was observed.

In total, 91 (40.1%) of these older adults had free full access to prescription drugs within the Brazilian National Health System. The median proportion of prescribed medications that were provided through the Brazilian National Health System was 83% (IQR = 33; minimum = 17 and maximum = 100). The median number of medicines accessed through the Brazilian National Health System was 4 (IQR = 3), and the median number of medicines accessed through private pharmacies was 1 (IQR = 1; minimum = 1 and maximum = 7). All the drugs used by 179 (78.9%) of these older adults were included in MEML.

The drugs used by the elderly people were predominantly from the following anatomical groups (level 1) of the ATC classification: group C – circulatory system (50.5%); group A – alimentary tract and metabolism (17.4%); and group N – nervous system (12.9%). On the other hand, analysis on drugs that were not included in RENAME and which were accessed through private pharmacies showed that the most frequent ATC groups were the following: group C (41.4%); group N (20.0%); and group B – blood and hematopoietic organs (12.9%) (**Table 2**). Univariate analysis on the associations between full access to medicines within the Brazilian National Health System and the independent variables (**Table 3**) showed that associations with the following factors were present at a 5% significance level: female, age ≤ 70 years, married, polypharmacy, multimorbidity and cardiovascular disease.

In the final logistic regression model, the presence of polypharmacy (odds ratio, OR = 0.47; confidence interval, CI = 0.268-0.838) and multimorbidity (OR = 0.26; CI = 0.087-0.775) was negatively associated with full access to medicines within the Brazilian

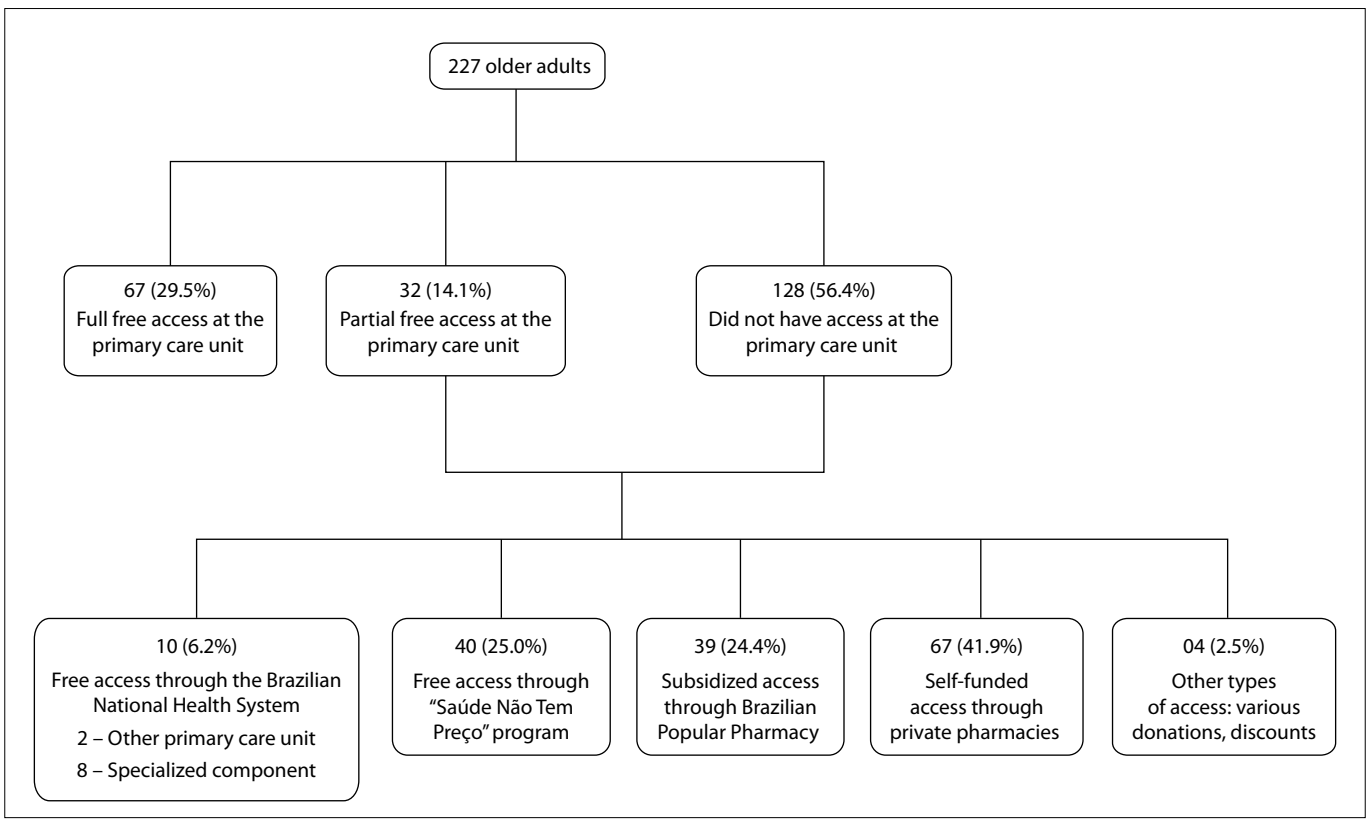

Figure 1. Characterization of access to medicines among the 227 older adults.

Table 2. Medicines acquired outside of the municipal essential medicines list (MEML)

Anatomical Therapeutic Chemical classification	All medicines		Medicines not included in the municipality essential medicines list	n	%
	n	%	Drug name		
Group A – Alimentary tract and nutrition	**206**	**17.4**		**8**	**11.4**
Drugs for peptic ulcer and gastroesophageal reflux disease			Pantoprazole	1	
Constipation drugs			Senna	1	
Insulin and analogues			Insulin glargine	2	
Blood glucose-lowering drugs, excluding insulin			Glimepiride	1	
			Sitagliptin	2	
Vitamins A and D, including associations			Vitamin D	1	
Group B - Drugs acting on blood and hematopoietic organs	**95**	**8.0**		**9**	**12.9**
Antithrombotic agents			Clopidogrel	4	
			Dabigatran	1	
			Cilostazol	1	
Vitamin B12 and folic acid			Cyanocobalamin	3	
Group C - Circulatory system drugs	**597**	**50.5**		**29**	**41.4**
Low-power thiazide diuretics			Chlorthalidone	2	
			Indapamide	3	
Hair-stabilizing agents			Diosmin	1	
			Troxerutin	1	
Beta-blocking agents			Pindolol	1	
			Metoprolol	3	
			Nebivolol	1	
Lipid-modifying agents			Atorvastatin	6	
			Pravastatin	1	
			Rosuvastatin	5	
			Fenofibrate	2	
Other cardiac preparations			Ivabradine	1	
Agents acting on the renin-angiotensin system			Telmisartan	2	
Group D - Dermatological drugs	**8**	**0.7**		**2**	**2.9**
Chemotherapy agents for topical use			Silver sulfadiazine	1	
Enzymes			Collagenase	1	
Group G – Genitourinary system and sex hormones	**1**	**0.1**	-	-	-
Group H - Systemic hormones, except sex hormones and insulins	**43**	**3.6**		**2**	**2.9**
Corticosteroids for systemic use			Fludrocortisone	1	
Anti-thyroid preparations			Thiamazole	1	
Group J- Anti-infective drugs for systemic use	**14**	**1.2**	-	-	-
Group M - Drugs acting on the musculoskeletal system and gout	**43**	**3.6**		**4**	**5.7**
Non-steroidal anti-inflammatory and anti-rheumatic products			Glucosamine	1	
			Meloxicam	1	
Central-action agents, muscle relaxants			Carisoprodol	1	
Drugs affecting bone structure and mineralization			Risedronate	1	
Group N - Nervous system drugs	**153**	**12.9**		**14**	**20**
Opioids			Codeine	1	
			Tramadol	1	
Antiepileptics			Lamotrigine	1	
Antipsychotics			Pimozide	1	
Anxiolytics			Alprazolam	1	
Hypnotics and sedatives			Nitrazepam	1	
Antidepressants			Citalopram	3	
			Escitalopram	1	
			Sertraline	2	
Anti-vertigo preparations			Betahistine	1	
Group R - Respiratory system drugs	**19**	**1.6**	Nasal decongestants	**1**	**1.4**
Group S – Sensory system drugs	**3**	**0.3**	Artificial tears	**1**	**1.4**
Total	**1,182**	**100**		**70**	**100**

National Health System. Age ≤ 70 years (OR = 1.92; CI = 1.092-3.380) was positively associated with full access to medicines in the Brazilian Unified Health System (**Table 3**).

DISCUSSION

This study showed that 40% of the older adults surveyed had free full access to prescription drugs within the Brazilian National

Table 3. Univariate and multivariate analysis on the factors associated with free full access to medicines within the Brazilian National Health System

Description	Full free access		Univariate analysis		Multivariate analysis	
Variable	Yes n (%)	No n (%)	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Sociodemographic factors						
Gender						
Female	57 (35.4)	104 (64.6)	0.52 (0.289-0.922)	**0.024**		
Male	34 (51.5)	32 (48.5)	1			
Age						
≤ 70 years	53 (46.5)	61 (53.5)	1.72 (1.003-2.932)	**0.048**	1.92 (1.092-3.380)	0.024
> 70 years	38 (33.6)	75 (66.4)	1		1	
Income						
> 2 minimum monthly wages	34 (40.5)	50 (59.5)	1.07 (0.610-1.867)	0.821		
≤ 2 minimum monthly wages	51 (38.9)	80 (61.1)	1			
Living alone						
No	70 (40.5)	103 (59.5)	1.07 (0.571-1.997)	0.837		
Yes	21 (38.9)	33 (61.1)	1			
Married						
Yes	42 (48.8)	44 (51.2)	1.79 (0.323-0.968)	**0.037**		
No	48 (34.8)	90 (65.2)	1			
Functional factors						
Instrumental activities of daily living						
Independent	25 (48.1)	27 (51.9)	1.529 (0.819-2.854)	**0.181**		
Partially dependent	66 (40.1)	136 (59.9)	1			
Basic activities of daily living						
Independent	73 (42.2)	100 (57.8)	1.419 (0.746-2.702)	0.285		
Dependent in at least one activity	18 (34.0)	35 (66.0)	1			
Clinical factors						
Self-perceived health						
Positive	63 (39.9)	95 (60.1)	0.947 (0.531-1.689)	0.855		
Negative	28 (41.2)	40 (58.8)	1			
Arterial hypertension						
Yes	79 (40.3)	117 (59.7)	1.069 (0.492-2.325)	0.866		
No	12 (38.7)	19 (61.3)	1			
Diabetes mellitus						
Yes	24 (32.4)	50 (67.6)	0.616 (0.44-1.103)	**0.102**		
No	67 (43.8)	86 (56.2)	1			
Cardiovascular diseases						
Yes	24 (31.2)	53 (68.8)	0.561 (0.314-1.002)	**0.049**		
No	67 (44.7)	83(55.3)	1			
Asthma and chronic obstructive pulmonary disease						
Yes	10 (29.4)	24 (70.6)	0.576 (0.261-1.271)	**0.168**		
No	81 (42.0)	112 (58)	1			
Multimorbidity						
Yes	78 (37.3)	131 (62.7)	0.229 (0.079-0.667)	**0.04**	0.26(0.087-0.775)	0.016
No	13 (72.2)	5 (27.8)	1			
Pharmacotherapeutic factors						
Polypharmacy						
Yes	44 (33.1)	89 (66.9)	0.494 (0.287-0850)	**0.01**	0.47(0.268-0.838)	0.01
No	47 (50.0)	47 (50.0)	1		1	

Hosmer and Lemeshow test: chi-square = 4.780; degrees of freedom = 4; P = 0.311.

Health System. Given the greater burden of noncommunicable diseases among elderly people, ensuring access to drugs for this age group in order to provide more effective control of these diseases, thereby contributing towards improving the capacity of actions provided to this population to resolve problems, is a priority. Among the guidelines and constitutional principles of the Brazilian State is that it guarantees comprehensive therapeutic care. Therefore, access to medicines is a citizen's right.[4]

The proportion of individuals with free full access to medicines within the Brazilian National Health System has ranged from 45.1% to 50.0% in investigations based on data obtained from the National Survey on Drug Access, Use and Promotion of Rational Use[4] and the National Household Sample Survey (NHSS).[9,11] The prevalence findings from the present study are in line those from other Brazilian studies, but comparisons should be made with caution because of methodological variations and inclusion criteria, given that the drug access survey and the study by Boing[11] using NHSS data did not include older adults alone.

Despite the strategies implemented to conform with the guidelines of the National Drug Policy and the National Pharmaceutical Services Policy, investigations have shown that only about half of citizens with prescription drugs fully obtain them from the Brazilian National Health System.[4] An economic evaluation from the perspective of the public healthcare system showed that medicines supplied through the primary public healthcare services of municipalities in the state of Minas Gerais had lower cost than those supplied through the *Aqui tem Farmácia Popular do Brasil* (The Brazilian popular pharmacy program is here) program, in which the Ministry of Health subsidizes the drug cost and the user pays co-payment fees for certain drugs purchased from private pharmacies.[21] New evaluations on the effectiveness of expanding drug access policies such as free treatment for hypertension, diabetes and asthma through the popular pharmacy program may provide elements for increasing free access to medicines within the Brazilian National Health System.

Full access to medicines through healthcare centers was reported by around one-third of the older adults surveyed here. This shows that the availability of access needs to be streamlined to ensure drug provision and improve geographical accessibility. Thus, it is crucial to improve the management of pharmaceutical care to increase the effectiveness of free access to drugs for the population, and to improve the availability of medicines in public healthcare facilities.[4,7] Improved management will contribute towards easing the challenge that the Brazilian National Health System faces in ensuring universal and continuous access to medicines, with equity and a capacity to resolve problems for the population

Most of the medicines used by the elderly people studied here were included in the municipal essential medicines list (MEML). This is a positive aspect of the way in which pharmaceutical services have been organized. It contributes towards implementation of access expansion actions, given that this facilitates the scheduling and dispensing steps. It also contributes towards rational use of drugs, since medicines included in the MEML are generally safe and effective.

A study conducted in primary healthcare centers in Belo Horizonte found a positive association between presence of the drug in the MEML and user access to it in the PCU.[22] On the other hand, an analysis on drugs used by older adults that were not included in the MEML showed that from the perspective of elderly people's care, therapeutic gaps existed. Absences of drugs such as cyanocobalamin, citalopram, clopidogrel, sertraline and escitalopram, which do not have substitutes in the drug list of the municipality investigated, were identified. In providing care for older adults, it is essential to develop actions to promote rational use of medicines and to implement strategies to ensure access to safe medications that are appropriate for the specificities of drug therapy in this population group. It is essential to consider the specificities of the older adult population[23] in selecting drugs and also in relation to other stages of pharmaceutical services.

The feminization of aging,[24] as well as the greater use of medicines by women, explain the lower likelihood of free access to medicines that was found in our study. On the other hand, the higher likelihood of free access among married older adults that was also observed illustrates the notion that family support can contribute towards healthcare. This increases the likelihood of access through more significant support for seeking drug provision strategies.

Cardiovascular diseases contribute significantly towards the burden of disease among older adults.[4,25] They require the use of multiple medications, which thus reduces the likelihood of free full access. Some elderly people with cardiovascular diseases may require drugs that are not included in the MEML, in order to streamline therapeutic endpoints, and this also reduces the likelihood of access. Circulatory system drugs, along with those that act on blood and hematopoietic organs, are among the drugs excluded from the MEML, yet these drugs are widely used by older adults.

Free access to medications independently showed a direct association with age ≤ 70 years and indirect associations with polypharmacy and multimorbidity. The associations observed in relation to these factors can be explained by the fact that elderly people with higher numbers of chronic diseases demand more meaningful use of medicines, which reduces the likelihood of access to prescribed drugs.[13] Understanding the specificities of drug therapy among older adults, the determinants of their drug use and the factors associated with access is vital for enabling development of actions towards greater availability of drugs and for improving the quality of pharmaceutical services for this population group within the Brazilian National Health System.

One strength of this study was that it analyzed the factors associated with free access to medicines through considering the

pharmacotherapeutic, clinical and sociodemographic aspects of access. Thus, it provided elements to support evaluation of the way in which pharmaceutical services are organized within the Brazilian National Health System. This study therefore helps towards reducing the challenge of ensuring universal, equitable and problem-resolving access.

This study has some limitations. Firstly, it was conducted only in two PCUs in a single Brazilian city, which thus does not allow generalizations. Secondly, only older adults who attended the PCU to receive medications were selected for the study. This may have led to selection bias, with greater inclusion of individuals with lower degrees of frailty. Thirdly, the evaluation of access to medicines covered only the prescriptions held at the time of the interview. It may have been the case that, at that time, these older adults did not have all the prescriptions for the medicines that they were using, which would have induced bias regarding the number of medicines. Another limitation relates to the information about comorbidities, which was self-reported, thus reducing the quality of this clinical information.

Investigations on access to medicines are important because they provide elements for characterizing the healthcare system and for supporting policies and actions aimed at increasing access to priority groups such as older adults.[9]

CONCLUSION

Free access to medicines is determined by the demographic, clinical, and pharmacotherapeutic characteristics of elderly people. Age ≤ 70 years increases the likelihood of free access, and older adults with multimorbidity and polypharmacy use have a lower likelihood of free full access to medicines. Access to medicines within the Brazilian National Health System among the elderly people surveyed here was high, but less than half of them were covered by full free access to prescription drugs. The availability of drugs in the PCUs was insufficient, which thus compromised the provision of drugs to older adults and geographical accessibility. Identification of factors associated with free access to medication among the elderly provides elements for guiding the Brazilian National Health System in implementing actions to improve access, such as the restructuring of pharmaceutical services to meet the specificities of the older adult population.

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Translation, cross-cultural adaptation and validation of the Finnish Diabetes Risk Score (FINDRISC) for use in Brazilian Portuguese: questionnaire validity study

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ABSTRACT

BACKGROUND: The Finnish Diabetes Risk Score (FINDRISC) is a questionnaire that was developed by Finnish researchers to track the risk of diabetes.

OBJECTIVE: To translate, cross-culturally adapt and validate the FINDRISC for use in Brazilian Portuguese.

DESIGN AND SETTING: Questionnaire validity study conducted at a private university.

METHODS: The Brazilian version of the FINDRISC was developed through the processes of translation, back-translation, committee review and pre-testing. Test-retest reliability was measured using the intraclass correlation coefficient (ICC), kappa coefficient, standard error of measurement (SEM) and minimum detectable change (MDC). Internal consistency was measured using Cronbach's alpha. For construct validity, the total score of the FINDRISC was correlated with the Diabetes Knowledge Scale (DKN-A) and Diabetes Mellitus Risk Questionnaire (QRDM). Ceiling and floor effects were also evaluated in the present study.

RESULTS: For construct validity and floor and ceiling effect measurements, a total sample of 107 participants was used. For reliability, a subsample of 51 participants out of the total sample was used. We identified adequate values for reliability (kappa ≥ 0.79 and ICC = 0.98) and internal consistency (Cronbach's alpha = 0.84). Regarding the error inherent in the FINDRISC, we found SEM = 8.02% and MDC = 22.44%. There were significant correlations between the FINDRISC and the QRDM (r = 0.686) and DKN-A (r = -0.216). No ceiling or floor effects were found.

CONCLUSION: The Brazilian version of the FINDRISC has adequate psychometric properties that are in accordance with the best international recommendations.

INTRODUCTION

Recently, the International Diabetes Federation reported that the number of individuals with type 2 diabetes mellitus (T2DM) had increased worldwide, especially in Brazil, which placed this country in fifth place among the countries with the most people with diabetes mellitus.[1]

Given this reality, strategies are being sought in an attempt to easily and cost-effectively screen individuals with high potential to develop T2DM, in order to implement preventive measures against the onset of the disease. In this context, use of questionnaires has been an ally in screening for several other diseases.[2-5]

A few questionnaires directed towards people with T2DM have been validated for Brazilian Portuguese, including the Diabetes Quality of Life Measure,[6] Diabetes Mellitus Knowledge and Attitude Questionnaire[5] and Diabetes Self-Care Activities.[7] With regard to the risk of developing T2DM, there is no validated questionnaire for use in Brazilian Portuguese for these purposes.

The Finnish Diabetes Risk Score (FINDRISC) is a questionnaire that was developed in Finnish and English in 2003 by Finnish researchers. It had the aims of tracking the risk of diabetes and stimulating the adoption of measures to prevent the onset of T2DM, especially for individuals who are at increased risk of the disease, but without the need for low-cost laboratory tests.[8] Some articles using the FINDRISC have already been published in Brazilian Portuguese,[9,10] even without proper translation, cross-cultural adaptation or validation of the questionnaire for this language. However, the FINDRISC has already been validated for other languages, including those spoken by the populations of Spain,[11] Greece,[12] Venezuela,[13] Colombia,[14] Hungary,[15] Germany,[16] Jordan,[17] China,[18] Norway[19] and Slovenia.[20]

OBJECTIVE

Considering the importance of instruments that track the risk of developing T2DM, for the context of public health, the aim of this study was to translate, cross-culturally adapt and validate the FINDRISC for use in Brazilian Portuguese.

METHODS

Study design and ethics

This was a cross-sectional study on the translation, cross-cultural adaptation and validation of a questionnaire. It was conducted in accordance with the Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures[21] and the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN).[22] Authorization for analysis of the psychometric properties of the FINDRISC in Brazilian Portuguese was granted via e-mail by the authors of the original version of the questionnaire (Dr. Jaana Lindstrom and Dr. Jaakko Tuomilehto).

This study was approved by the Research Ethics Committee of our institution, under number 2.853.570, on August 29, 2018. All the participants validated their participation by signing a free and informed consent statement. These participants were recruited from the university community in the city of São Luís (MA), Brazil, and from a community associated with this city. Announcements regarding this study were disseminated through pamphlets and social media.

FINDRISC translation and cross-cultural adaptation

The process of translation and cross-cultural adaptation of the FINDRISC for use in Brazilian Portuguese followed the criteria of Beaton et al.[21] and was performed in five phases as described below:

1) Translation: two independent translators, both with Brazilian Portuguese as their mother tongue and fluent in English, translated the original version of the questionnaire into Brazilian Portuguese;
2) Synthesis of translations: after discussions and revisions, the two translators, under observation of one of the researchers, produced a synthesis from the two versions of the independently translated questionnaire, thus resulting in a combined version in a consensual manner;
3) Back-translation: two independent translators (without technical knowledge of health issues), both with English as the mother tongue and fluent in Portuguese, translated the Portuguese version of the questionnaire back to English, without previous knowledge of the original version of the questionnaire;
4) Expert committee review: six diabetes specialists, along with the four translators of this study, reviewed the original version and the translated, synthetized and back-translated versions, and defined the pre-final version of the FINDRISC;
5) Pre-final version test: the pre-final version of the questionnaire was administered to 30 individuals without a diagnosis of diabetes and with Portuguese as their mother tongue. The respondents' comprehension of the items and responses in the FINDRISC was evaluated.

Participants

The sample size for this validation study was based on COSMIN, and a minimum of 100 individuals was recommended.[23] The eligibility criteria that we used were that the participants could be of either sex, without any diagnosis of type 1 or type 2 diabetes mellitus, aged over 24 years and under 64 years, and without cognitive deficits or any other limitations that would make it impossible for them to respond to the questionnaire.

FINDRISC

The FINDRISC consists of eight items that investigate and rate the risk of developing T2DM within 10 years. The responses to each item are scored according to their influence on the development of the disease. The total score can range from 0 to 26 points and is classified as follows: ≤ 7 points, low risk (1 in 100 people will develop disease); 7 to 11 points, slightly elevated risk (1 in 25 people will develop the disease); 12 to 14 points, moderate risk (1 in 6 people will develop the disease); 15 to 20 points, high risk (1 in 3 people will develop the disease); and > 20 points, very high risk (1 in 2 people will develop the disease).

OTHER QUESTIONNAIRES

In addition to the FINDRISC, we applied two other questionnaires that had already been adapted and validated for use in Brazilian Portuguese, to ascertain the construct validity. These instruments were:

1) Diabetes Knowledge Scale (DKN-A), a questionnaire that was validated for the Brazilian population by Torres et al.,[5] which is composed of 15 multiple-choice questions on various aspects of general knowledge relating to T2DM. The total score is calculated by assigning one point to each correct answer, and it can range from 0 to 15. The higher the score is, the greater the respondent's knowledge about T2DM is.
2) Diabetes Mellitus Risk Questionnaire (QRDM), a questionnaire that was validated in the master's degree dissertation of Cruz,[3] which is composed of seven items, with a total score that can range from 0 to 27 points. The higher the score is, the higher the respondent's risk of developing T2DM is.

Statistical analysis

Reliability was assessed based on a test-retest model by measuring the kappa coefficient, intraclass correlation coefficient (ICC), standard error of measurement (SEM) and minimum

detectable change (MDC). Internal consistency was assessed using Cronbach's alpha. The kappa values were interpreted based on the categories defined by Sim and Wright: < 0, poor; 0.01-0.20, slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; and 0.81-1, almost perfect.[24] The ICC values were interpreted based on the study by Fleiss: for values below 0.40, reliability was considered low; between 0.40 and 0.75, moderate; between 0.75 and 0.90, substantial; and greater than 0.90, excellent.[25] The SEM percentage was interpreted based on the definitions of Ostelo et al.: 5% or less, very good; greater than 5% and less than or equal to 10%, good; greater than 10% and less than or equal to 20%, doubtful; and greater than 20%, negative.[26]

To ascertain the validity of the construct, Pearson's correlation coefficient (r) was used to determine the magnitude of the correlations between the FINDRISC and the QRDM, and between the FINDRISC and the DKN-A. The r values were interpreted in accordance with the COSMIN recommendations: correlations with instruments measuring similar constructs should be ≥ 0.50; correlations with instruments measuring related but dissimilar constructs should be 0.30-0.50; and correlations with instruments measuring unrelated constructs should be < 0.30.[22]

Ceiling and floor effects were evaluated in the present study. By definition, these effects occurred when a number of study participants (set as over 15%) reached the minimum or maximum values of the total score of the questionnaire.

RESULTS

Sample characterization

The study consisted of three samples of different sizes. Initially, for the analysis on the pre-test version of the instrument, 30 participants were included. For the assessment of construct validity and measurement of the floor and ceiling effects, a total sample consisting of 107 participants who were evaluated at a single time was used. For determine the reliability of the FINDRISC, a subsample was used, comprising 51 participants from the total sample who were evaluated at two times (test and retest), seven days apart. The sample size used in this validation study was in accordance with international practices for cross-cultural adaptation and validation of questionnaires, as guided by the study of Beaton et al.[21] and by COSMIN.[22]

The participants' characteristics are described in **Table 1**, along with the mean scores from the QRDM and DKN-A questionnaires.

Translation and cross-cultural adaptation

The translation and back-translation processes are described in **Table 2**. After the two translations performed by Portuguese native speakers, the translations were synthetized, and the translators came to an agreement regarding the definitions for the eight items of the FINDRISC in Brazilian Portuguese. Next, back-translation was performed by two English native speakers. After this phase, there was a meeting involving the translators and a committee of experts, and the synthetized version was accepted unanimously, without any amendments proposed. In this manner, the pre-final version of the FINDRISC was defined.

The pre-final version of the FINDRISC was applied to 30 individuals (24 women, 80%) without a diagnosis of diabetes and with Brazilian Portuguese as their mother tongue. The average age of this sample was 49 years (standard deviation, SD = 10.82), and the average FINDRISC score was 11.56 points (SD = 4.70). There was 100% understanding of the questionnaire items, which thus defined the final version of the FINDRISC in Brazilian Portuguese (Appendices 1 and 2).

Reliability and internal consistency

Table 3 presents the reliability values item-by-item and the total score of the final version of the FINDRISC in Brazilian Portuguese. We found adequate values for reliability (kappa ≥ 0.66 and ICC = 0.98) and internal consistency (Cronbach's alpha ≥ 0.82). In addition, in calculating the error inherent to the FINDRISC total score, we found that the values were sufficient, as follows: SEM (absolute) = 0.63; SEM (%) = 8.02; MDC (absolute) = 1.76; and MDC (%) = 22.44.

Construct validity

The construct validity was tested by correlating the total FINDRISC score with the scores from the other questionnaires

Table 1. Characteristics of study participants according to study phase

Characteristic	Reliability phase (n = 51)	Validity phase (n = 107)
Gender (female)[a]	38 (74.51%)	80 (74.8%)
Age (years)[b]	36.90 (10.67)	42.88 (12.35)
Schooling[a]		
Elementary education	3 (5.9%)	18 (16.9%)
High school	30 (58.8%)	59 (55.1%)
Higher education	18 (35.3%)	30 (28%)
Marital status[a]		
Single	35 (68.6%)	60 (56.1%)
Married	14 (27.4%)	43 (40.2%)
Divorced	1 (2.0%)	2 (1.9%)
Widowed	1 (2.0%)	2 (1.9%)
Height (m)[b]	1.59 (0.24)	1.59 (0.18)
Weight (kg)[b]	67.62 (12.18)	68.09 (12.61)
BMI (kg/m²)[b]	25.58 (3.93)	26.26 (4.46)
Abdominal circumference (cm)[b]	84.52 (12.00)	87.48 (12.48)
QRDM (score)[b]	7.80 (5.16)	9.27 (5.30)
DKN-A (score)[b]	7.94 (2.58)	7.63 (2.69)

[a]Values presented as absolute number (percentage); [b]Values presented as mean (standard deviation).

BMI = body mass index; QRDM = Diabetes Mellitus Risk Questionnaire; DKN-A = Diabetes Knowledge Scale.

of the present study. The following significant ($P < 0.05$) and adequate correlations with this validation criterion were observed: QRDM (r = 0.686) and DKN-A (r = -0.216). According to COSMIN, values ≥ 0.50 are expected for correlations of questionnaire scores with similar constructs (as in the case of QRDM) and values < 0.30 for correlations of questionnaire scores with unrelated constructs (as in the case of DKN-A).

Ceiling and floor effects

Two individuals (1.9%) achieved a FINDRISC minimum score of 0. No participant reached the maximum score of 26 points. Therefore, ceiling and floor effects were not observed.

DISCUSSION

We observed that the FINDRISC in Brazilian Portuguese presented an adequate level of comprehension in the study population and acceptable values for reliability, internal consistency and validity. Regarding reliability, our study found kappa values (when considered item-by-item) ranging from 0.66 to 1.00 and ICC values (when considering the total score) of 0.98. In addition, Cronbach's alpha of 0.84 was found. Significant correlations were found between the FINDRISC and DKN-A and between the FINDRISC and QRDM.

The FINDRISC has also been considered to be a valid questionnaire in other countries. However, these validations did not

Table 2. Translation, consensus version and backtranslation of Finnish Diabetes Risk Score (FINDRISC)

Original version of FINDRISC		Translation	Consensus version	Backtranslation
Number	**Item**			
1	Age.	T1: Idade. T2: Idade.	T12: Idade.	B1: Age. B2: Age.
2	Body mass index.	T1: Índice de massa corporal (IMC). T2: Índice de massa corporal.	T12: Índice de massa corporal (IMC).	B1: Body mass index (BMI). B2: Body mass index (BMI).
3	Waist circumference measured below the ribs (usually at the level of the navel).	T1: Circunferência da cintura medida abaixo das costelas (geralmente na altura do umbigo). T2: Medida da cintura (geralmente ao nível do umbigo).	T12: Circunferência da cintura medida abaixo das costelas (geralmente na altura do umbigo).	B1: Waist circumference measured below the ribs (generally at the height of the navel). B2: Waist circumference measured below the ribs (generally at height of belly button).
4	Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (including normal daily activity)?	T1: Você costuma ter pelo menos 30 minutos de atividade física diária no trabalho e/ou durante o horário de lazer (incluindo as atividades diárias normais)? T2: Pratica, diariamente, atividade física pelo menos durante 30 minutos, no trabalho ou durante o tempo livre (incluindo atividades da vida diária)?	T12: Você pratica pelo menos 30 minutos de atividade física diária no trabalho e/ou durante o horário de lazer (incluindo as atividades diárias normais)?	B1: Do you practice at least 30 minutes of daily physical activity at work and/or during leisure time (including normal daily activities)? B2: Do you practice at least 30 minutes of daily physical activity at work and/or during leisure time (including normal daily activities)?
5	How often do you eat vegetables, fruit or berries?	T1: Com que frequência você come legumes e verduras, frutas ou grãos? T2: Com que frequência você consome vegetais ou frutas?	T12: Com que frequência você come legumes, verduras, frutas ou grãos?	B1: How often do you eat legumes, vegetables, fruit or grains? B2: How often do you eat vegetables, fruits, or grains?
6	Have you ever taken medication for high blood pressure on regular basis?	T1: Você já tomou alguma medicação para pressão alta regularmente? T2: Já tomou regularmente algum medicamento para pressão alta?	T12: Você já tomou regularmente algum medicamento para pressão alta?	B1: Do you regularly take any medication for high blood pressure? B2: Have you ever taken any medication for high blood pressure?
7	Have you ever been found to have high blood glucose (e.g. in a health examination, during an illness, during pregnancy)?	T1: Alguma vez você já apresentou glicose alta no sangue (exemplo: em um exame médico, durante uma doença, durante gravidez)? T2: Alguma vez teve açúcar elevado no sangue (por ex: em exame de rotina, durante alguma doença, na gravidez)?	T12: Alguma vez você já apresentou glicose alta no sangue (por exemplo, em um exame médico de rotina, durante uma doença, durante gravidez)?	B1: Have you ever had high blood glucose (for example, at a routine medical examination, during an illness, during pregnancy)? B2: Have you ever had high blood glucose (for example, during a routine medical examination, during illness, during pregnancy)?
8	Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?	T1: Algum membro de sua família imediata ou outro parente já foi diagnosticado(a) com diabetes (tipo 1 ou tipo 2)? T2: Algum membro da sua família ou parente próximo já foi diagnosticado com diabetes (tipo 1 ou 2)?	T12: Algum membro de sua família ou parente próximo já foi diagnosticado com diabetes (tipo 1 ou tipo 2)?	B1: Has any member of your family or close relative ever been diagnosed with diabetes (type 1 or type 2)? B2: Has any member of your immediate family or relative ever been diagnosed with diabetes (type 1 or type 2)?

T1 = translation 1; T2 = translation 2; T12 = consensual synthesis of translations 1 and 2; B1 = backtranslation 1; B2 = backtranslation 2.

Table 3. Finnish Diabetes Risk Score (FINDRISC) reliability and internal consistency with presentation of mean values, standard deviation (SD), kappa or intraclass correlation coefficient (ICC) with 95% confidence interval (CI) and Cronbach's alpha

FINDRISC item	Mean (SD)		Reliability	Cronbach's alpha if item excluded
	Test	Retest		
1	0.58 (1.10)	0.56 (1.10)	kappa = 1.00 (95% CI = 1.00, 1.00)	0.83
2	0.88 (1.03)	0.88 (1.06)	kappa = 1.00 (95% CI = 1.00, 1.00)	0.83
3	1.96 (1.76)	1.90 (1.78)	kappa = 0.90 (95% CI = 0.85, 0.95)	0.82
4	1.01 (1.00)	1.17 (0.99)	kappa = 0.68 (95% CI = 0.61, 0.74)	0.84
5	0.60 (0.80)	0.54 (0.50)	kappa = 0.72 (95% CI = 0.65, 0.78)	0.84
6	0.11 (0.47)	0.11 (0.47)	kappa = 1.00 (95% CI = 1.00, 1.00)	0.84
7	0.09 (0.70)	0.19 (0.98)	kappa = 0.66 (95% CI = 0.46, 0.86)	0.84
8	2.70 (2.10)	2.70 (2.10)	kappa = 1.00 (95% CI = 1.00, 1.00)	0.83
Total score	7.82 (4.32)	8.01 (4.66)	ICC = 0.98 (95% CI = 0.97, 0.99)	Cronbach's alpha = 0.84

have cross-cultural translation and adaptation, and only tested the accuracy of diagnosing the risk of developing diabetes based on FINDRISC cutoff points. All of these studies used the receiver operating characteristic (ROC) curve as a statistical method. Thus, the following findings were observed: area under the ROC curve of 0.77 in Norway,[19] greater than 0.70 in Venezuela, of 0.78 in Slovenia,[20] of 0.74 in Mexico,[27] of 0.76 in China,[18] greater than 0.72 in Greece[12] and greater than 0.74 in Spain.[11] It is noteworthy that the values for the area under the ROC curve that were identified in these various studies established that the degree of accuracy of the FINDRISC was adequate.

The international best practices for translation, cross-cultural adaptation and validation of questionnaires are centered on COSMIN.[22] These methodological guidelines indicate several psychometric properties that an instrument should present, with emphasis on i) reliability and ii) validity (composed of several subitems, such as face, content, construct, structural, cross-cultural and criterion validity) and responsiveness. Our validation study involved assessments of reliability (using kappa, ICC, SEM and MDC), cross-cultural adaptation (using translation, synthesis of translations, back-translation, expert committee and pre-final testing), construct validity (using the correlation between questionnaires) and structural validity (using Cronbach's alpha). These properties ensured that the FINDRISC can be applied to the Brazilian population. Other questionnaire validation studies conducted in Brazil have also measured these psychometric properties.[28–30]

Some limitations of this study and suggestions need to be noted. Firstly, we recommend that the cross-cultural adaptation of the FINDRISC to other languages should be tested based on COSMIN.[22] Lack of such testing greatly limited the discussion of the results. In addition, because of the need for specific methodology, our study did not investigate the accuracy or responsiveness of the FINDRISC. Thus, we suggest that future studies should measure these psychometric properties in Brazilian Portuguese.

CONCLUSION

The results from this study demonstrate that the Brazilian Portuguese version of the FINDRISC has adequate psychometric properties that are in accordance with the best international recommendations. Thus, its use within clinical routines and/or research can be supported.

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Appendix 1. Brazilian Portuguese version of Finnish Diabetes Risk Score (FINDRISC), initial page.

AVALIAÇÃO DE RISCO DE DIABETES TIPO 2

Circule a alternativa correta e some os seus pontos.

1. Idade

0 p. Abaixo de 45 anos
2 p. Entre 45-54 anos
3 p. Entre 55-64 anos
4 p. Acima de 64 anos

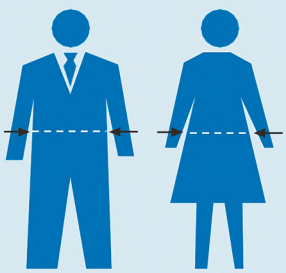
2. Índice de massa corporal (IMC)

(Ver verso do formulário)

0 p. Abaixo de 25kg/m²
1 p. 25-30kg/m²
3 p. Acima de 30kg/m²

3. Circunferência da cintura medida abaixo das costelas (geralmente na altura do umbigo)

	HOMENS	MULHERES
0 p.	Menor que 94 cm	Menor que 80 cm
3 p.	94-102 cm	80-88 cm
4 p.	Maior que 102 cm	Maior que 88 cm



4. Você pratica pelo menos 30 minutos de atividade física diária no trabalho e/ou durante o horário de lazer (incluindo as atividades diárias normais)?

0 p. Sim
2 p. Não

5. Com que frequência você come legumes, verduras, frutas ou grãos?

0 p. Todos os dias
1 p. Não todos os dias

6. Você já tomou regularmente algum medicamento para pressão alta?

0 p. Não
2 p. Sim

7. Alguma vez você já apresentou glicose alta no sangue (por exemplo, em um exame médico de rotina, durante uma doença, durante gravidez)?

0 p. Não
5 p. Sim

8. Algum membro de sua família ou parente próximo já foi diagnosticado com diabetes (tipo 1 ou tipo 2)?

0 p. Não
3 p. Sim: avós, tia, tio ou primo de 1° grau (exceto pai, mãe, irmão, irmã ou filhos)
5 p. Sim: pai, mãe, irmão, irmã ou filho

Pontuação Total de Risco

☐ **O risco de desenvolver diabetes tipo 2 em 10 anos é:**

Menor que 7	**Baixo:** cerca de 1 em cada 100 pessoas irá desenvolver a doença
7-11	**Levemente elevado:** cerca de 1 em cada 25 pessoas irá desenvolver a doença
12-14	**Moderado:** cerca de 1 em cada 6 pessoas irá desenvolver a doença
15-20	**Alto:** cerca de 1 em cada 3 pessoas irá desenvolver a doença
Maior que 20	**Muito alto:** cerca de 1 em cada 2 pessoas irá desenvolver a doença

Por favor, olhe o verso

Appendix 2. Brazilian Portuguese version of Finnish Diabetes Risk Score (FINDRISC), final page.

O QUE VOCÊ PODE FAZER PARA DIMINUIR O SEU RISCO DE DESENVOLVER DIABETES TIPO 2?

Você não pode mudar sua idade ou sua predisposição genética. Entretanto, os outros fatores que predispõem ao diabetes, como sobrepeso, gordura abdominal, sedentarismo, hábitos alimentares e o hábito de fumar, dependem de você. Suas escolhas de estilo de vida podem evitar o diabetes tipo 2 ou pelo menos retardá-lo até uma idade mais avançada.

Caso haja alguém com diabetes na sua família, você deve atentar para não ganhar peso com o passar dos anos. O aumento da circunferência abdominal, em particular, aumenta o risco do diabetes, enquanto que a atividade física moderada diminui o risco. Você deve também ficar atento à sua dieta: consuma muitos produtos à base de cereais ricos em fibras e legumes todos os dias. Evite o excesso de gordura na sua dieta.

Os primeiros estágios do diabetes tipo 2 raramente apresentam sintomas. Se o seu total de pontos foi de 12 a 14 na Avaliação de Risco, você deve avaliar seriamente suas atividades físicas e hábitos alimentares e prestar atenção ao seu peso, para prevenir o desenvolvimento do diabetes. Não deixe de consultar o seu médico para mais informações e testes.

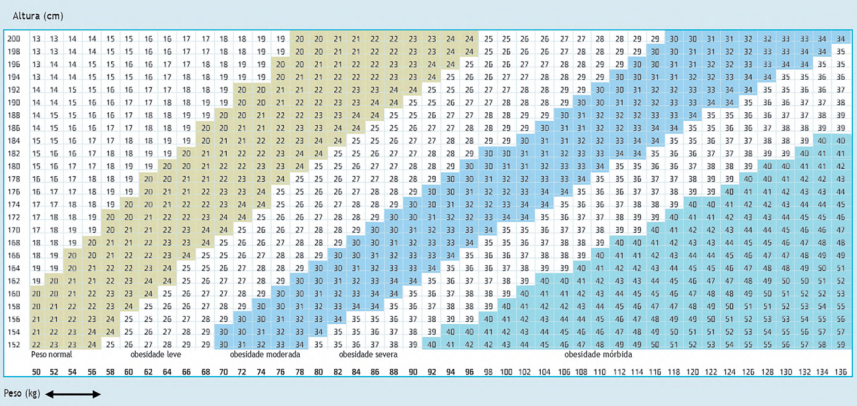
Se o seu total de pontos foi 15 ou mais na Avaliação de Risco, você deve fazer o teste de glicemia (em jejum e depois de uma dose de glicose ou após uma refeição) para determinar se você tem diabetes sem sintomas.

ÍNDICE DE MASSA CORPORAL (IMC)

O índice de massa corporal é usado para avaliar se uma pessoa está com o peso normal ou não. O índice é calculado dividindo-se o peso corporal (kg) pela altura ao quadrado (m). Por exemplo, se a sua altura é 1,65 m e seu peso é 70 kg, seu índice de massa corporal será 70/(1,65 x 1,65), o que resulta em 25,7.

Se o seu índice de massa corporal estiver entre 25 e 30, você se beneficiará se perder peso ou ao menos deve se prevenir para que o seu peso não ultrapasse o atual. Se o seu índice de massa corporal for maior que 30, os efeitos adversos da obesidade começarão a aparecer e será importante você perder peso.

TABELA: ÍNDICE DE MASSA CORPORAL



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Suicide mortality in the city of São Paulo: epidemiological characteristics and their social factors in a temporal trend between 2000 and 2017. Retrospective study

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KEY WORDS (MeSH terms):
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AUTHORS' KEY WORDS:
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ABSTRACT

BACKGROUND: Suicide is one of the leading causes of death worldwide, accounting for one million deaths annually. Greater understanding of the causal risk factors is needed, especially in large urban centers.

OBJECTIVE: To ascertain the epidemiological profile and temporal trend of suicides over two decades and correlate prevalence with social indicators.

DESIGN AND SETTING: Descriptive population-based longitudinal retrospective study conducted in the city of São Paulo, Brazil.

METHODS: A temporal trend series for suicide mortality in this city was constructed based on data from the Ministry of Health's mortality notification system, covering 2000-2017. It was analyzed using classic demographic variables relating to social factors.

RESULTS: Suicide rates were high throughout this period, increasing from 4.6/100,000 inhabitants in the 2000s to 4.9/100,000 in 2017 (mean: 4.7/100,000). The increase in mortality was mainly due to increased male suicide, which went from 6.0/100,000 to the current 8.0/100,000. Other higher coefficients corresponded to social risk factors, such as being a young adult (25-44 years old), being more educated (eight years of schooling) and having white ethnicity (67.2%). Suicide was also twice as likely to occur at home (47.8%).

CONCLUSION: High suicide rates were seen over the period 2000-2017, especially among young adults and males. High schooling levels and white ethnicity were risk factors. The home environment is the crucial arena for preventive action. One special aspect of primary prevention is the internet and especially social media, which provides a multitude of information for suicide prevention.

INTRODUCTION

Suicide is one of the three most common causes of death worldwide. The World Health Organization (WHO) has defined it as aggression or a violent act committed against one's own life, with the intention of death.[1] It is currently one of the most important public health problems and is often attributed to how its victims are affected by society and the collective environment in which they live.[2] It has several supporting risk factors, such as psychological, biological and social factors.[3]

Suicide is among the 20 leading causes of death worldwide in different age groups, including adolescents, adults and the elderly. One death by suicide occurs every 40 seconds somewhere in the world.[4] Findings from 2012 revealed that there were around 800,000 suicide deaths worldwide, representing an age-standardized overall annual rate of 11.4 per 100,000 inhabitants, within which males and the age group of young adults formed more significant components.[5]

In epidemiological studies, it has been estimated that by 2020, there will be a 50% increase in the annual incidence of suicide deaths worldwide, which could exceed the number of deaths from homicide and war.[6,7] Suicide rates have undergone exponential increases in several countries such as France, China, Switzerland, Belgium, Austria, the United States, Japan and Brazil, as well as in countries in Eastern Europe, which report suicide rates above 16 deaths per 100,000 inhabitants.[6,7] However, there is still great difficulty in assessing the dimensions of this problem and accurately recording suicidal acts.[8]

Globally, suicides are the second leading cause of premature mortality among individuals aged 15 to 29 years (preceded only by traffic accidents), and number three in the age group of 15-44 years.[9] Upsettingly, in 2015, the vast majority, i.e. namely 78% of suicides, were committed in low and middle-income countries (LMIC). High suicide rates also represent a financial burden to society, and

this is most markedly so when young and middle-aged men who are about to start or have just started their professional and family lives commit suicide.[9] In the United States, in the early 2010s, the costs per each single suicide were estimated to be over $1 million, while estimates from Ireland, Scotland and New Zealand lay between $2.1 and $2.5 million. In the literature, only 6% of the studies come from low-income countries low-income countries such as sub-Saharan Africa. Most studies have focused on measurements of poverty like unemployment and economic status, while neglecting dimensions such as debt, relative and absolute poverty, and support from welfare systems.[9,10] This opens up a huge gap between the overall numbers of suicides in LMIC (78% of suicides worldwide) and knowledge of costs within the respective societies.[9,10]

Considering the significance that suicide has and the public health crisis that it has precipitated, a detailed understanding of the different age groups, genders, ethnicities and places with higher prevalence of suicide in large urban centers (where the characteristics of the environment increase the risks of mental disorders, such as depression, anxiety and stress) is essential. Through this, monitoring can be promoted and possible strategies for reducing individuals' risk of suicide can be implemented.[11-13]

Although studies have shown that there has been a threefold increase in the suicide rate among males,[12] there are still no reports of this rate over the course of two decades, or 18 consecutive years. Nor are there any reports on its prevalence in specific age groups, among specific ethnicities or in places in emerging countries with large urban populations. This phenomenon results from a complex network of biological, genetic, psychological, sociocultural and economic interactions.[13]

Studies have shown that suicide rates are increasing, but most studies have investigated only specific periods of time, or regions and states.[14-16] However, greater specificity for actions and local preventive strategies is required.

OBJECTIVES

The aims of this study were to analyze the epidemiological profile and temporal trends of suicide cases in the city of São Paulo, Brazil, over two decades, and to analyze the prevalence of these cases in relation to social indicators.

METHODS

This was a mortality study (time series) that had the aim of characterizing aspects of suicide mortality in the city of São Paulo (SP), Brazil, from 2000 to 2017.

All the data used were obtained from official secondary sources. The number of suicides was obtained from the mortality information system (SIM) database and health information was obtained from a database (TABNET) maintained by the Brazilian Ministry of Health (DATASUS). The population of each state was obtained from the Brazilian Institute for Geography and Statistics (IBGE). Census data were taken from years in which censuses were performed, and were interpolated for the other years. These datasets are publicly available online.

Suicide was defined as death resulting from intentional self-harm, in accordance with the International Classification of Diseases, tenth edition (ICD-10), which uses codes X60 to X84 and Y87 to identify this outcome.

The 2000-2017 time series was composed of annual suicide rates. These were calculated as suicide mortality coefficients (using the numbers of occurrences divided by the general population per 100,000 inhabitants) and as standardized mortality (using the numbers of occurrences divided by the standardized population per 100,000 inhabitants) for the municipality of São Paulo. Analyses stratified according to sex, age group, education level, ethnicity and place where suicide was committed were also performed. Values corresponding to unknown age were excluded.

Statistical analysis

We used the SPSS software, version 10.0, to identify and estimate suicide rates and standardized mortality coefficients. To calculate mortality coefficients, population data and data on mortality due to external causes were used. The overall mortality coefficient is one of the indicators of the state of health of a population. For the purposes of comparing populations, standardization was indispensable for correcting distortions resulting from possible differences in their composition with respect to attributes or variables related to the probability of death.[17]

The median of the participation percentages, rather than the arithmetic mean, was used with the aim of removing the influence that, in this case, would be exerted by possible occurrences, in certain populations, of strongly disagreeing percentages of participation.[18] The denominator that was used to calculate the standardized coefficient was that of the standard population, which was calculated using the median population of the period studied. Historical series were built for the period from 2000 to 2017.

RESULTS

Over the 18 years that made up this analysis, there were 8,726 deaths due to suicide in the city of São Paulo, corresponding to 4.7 deaths per 100,000 inhabitants, while the world averages ranged from 3.5 to 4.0 deaths per 100,000 inhabitants.

The coefficients were standardized using the standard population provided by the World Health Organization (WHO). The gross coefficient of the population increased from 4.08/100,000 in 2000 to 4.69/100,000 in 2017. It also needs to be taken into account that, because of the taboo surrounding suicide, deaths due to this event may be reported as deaths due to an external cause of unknown type. This may have induced underreporting of the problem.

Table 1 shows the original and standardized suicide mortality rates for the municipality of São Paulo in this time series from 2000 to 2017. The standardized suicide mortality rates for both sexes increased from 3.84/100.000 in 2000 to 4.96/100.000 in 2017. The increase in the male standardized coefficient was from 6.08/100.000 in 2000 to 8.09/100.000 in 2017, while for females it increased from 1.91 to 1.97/100,000 over this same period. The male-to-female ratio increased from four in 2000 to six at the end of the study period, in 2017. The temporal trend showed that higher male rates were maintained throughout the study period, without any abrupt increase.

Table 2 shows the numbers of deaths, proportional mortality and suicide mortality coefficient according to age, education, ethnicity and place of suicide, in the 18 consecutive years of the period from 2000 to 2017. Higher proportions of suicides occurred among young adults (25 to 44 years old) and individuals with higher education (more than 8 years of schooling). However, the highest coefficient was for individuals of white ethnicity (67.2%) and for suicide occurrences at home (47.8%). The risk in the white population (2.91/100.000) was almost three times higher than in the other populations. In addition, another important finding was that the chance of suicide occurring at home was twice as high (2.07/100,000) as in other places, over the years.

DISCUSSION

The main objective of this study was to analyze the epidemiological profile and temporal trends of suicide cases in the city of São Paulo over two decades and to analyze the prevalence of suicide in relation to social indicators. The main finding was that there was a great number of deaths (8,726) due to suicide in the municipality studied, in comparison with other countries, corresponding to 4.7 deaths per 100,000 inhabitants, while the world average ranged from 3.5 to 4.0 deaths per 100,000 inhabitants. Another important finding was that there was an increase in the male standardized coefficient from 6.08/100,000 in 2000 to 8.09/100,000 in 2017. Regarding social indicators, there were higher proportions of suicides among young adults (25-44 years), individuals with higher education and individuals of white ethnicity. The place where most suicides were committed was the home, which was twice as high as in other places, over the years.

In Brazil, the average mortality rate due to suicide over the period 2004-2010 was 5.7%.[19,20] Over the last two decades (2000-2017), this rate was lower in the city of São Paulo (4.7), but compared with other countries, it can still be considered high and of significant impact. The world average ranged from 3.5 to 4.0, and the coefficients found in European countries were at this average level. The lowest coefficients were in Central and South American countries, while the coefficients in the United States, Australia, Japan and Central European countries were in an intermediate range.[14,21]

The differential of the present study was that a suicide rate of 4.7 was ascertained in a single municipality. This urban center can be considered to be a reference point, given its large population. The results from this city showed that there is a need for greater support for preventive and management actions within public policies.

Table 1. Mortality coefficients relating to crude and standardized suicide, according to sex and total data. São Paulo (SP), 2000-2017

Years	Death (male)	Male sex coefficient Mortality suicide		Death (female)	Female sex coefficient Mortality suicide		Death (All)	Coefficient mortality suicide	
		Original	Standardized		Original	Standardized		Original	Standardized
2000	321	6.46	6.08	104	1.91	1.78	425	4.08	3.84
2001	311	6.20	5.89	107	1.94	1.83	418	3.97	3.78
2002	305	6.04	5.78	90	1.62	1.54	395	3.72	3.57
2003	321	6.31	6.08	94	1.68	1.61	415	3.88	3.75
2004	303	5.91	5.74	97	1.72	1.66	400	3.71	3.62
2005	334	6.47	6.33	121	2.12	2.07	455	4.19	4.12
2006	376	7.23	7.13	94	1.64	1.61	470	4.29	4.25
2007	379	7.25	7.18	113	1.95	1.93	492	4.46	4.45
2008	392	7.45	7.43	106	1.82	1.81	498	4.49	4.50
2009	394	7.44	7.47	122	2.08	2.08	516	4.62	4.67
2010	400	7.51	7.58	130	2.20	2.22	530	4.71	4.79
2011	409	7.63	7.75	129	2.17	2.20	538	4.76	4.87
2012	407	7.54	7.71	154	2.57	2.63	561	4.93	5.07
2013	396	7.29	7.50	146	2.43	2.49	542	4.74	4.90
2014	401	7.34	7.60	133	2.20	2.27	534	4.64	4.83
2015	388	7.05	7.35	140	2.30	2.39	528	4.56	4.78
2016	365	6.60	6.92	96	1.57	1.64	461	3.96	4.17
2017	427	7.68	8.09	121	1.97	2.07	548	4.69	4.96
Total	**6,629**	**6.98**	**6.97**	**2,097**	**2.00**	**1.99**	**8,726**	**4.70**	**4.97**

Another important point observed in this study was that the suicide mortality rate was higher among males (standardized coefficient of 8.09/100,000). Thus, men committed suicide almost twice as often as women in the city of São Paulo, Brazil, over the 18-year period 2000-2017. However, comparison of information from 183 countries shows that the male-to-female ratio varies.[9] Several studies have documented the epidemiology of higher suicide rates among males, which in some countries have reached a ratio of 3:1.[14,19] Higher rates have also been observed in small and medium-sized cities and municipalities.[20,22] One exception is India and China, where the suicide rate among females exceeds that of males.[23]

The findings of the present study showed that there was higher prevalence of suicide among males than among females. The explanation for this, according to some authors,[24-26] relates to manifestations of masculinity, which involves behaviors that predispose towards suicide, such as competitiveness, impulsivity and greater access to lethal weapons, including firearms.

In addition, failure to fulfill traditional gender roles, which for men means being the economic provider for the family, generates greater stress and anxiety. Men who live within a patriarchal culture are more sensitive to economic setbacks such as unemployment and impoverishment and more prone to suicide.[25] This was corroborated by the higher rates and temporal trends seen among men in this large-sized city, over the 18 years evaluated in the present study. The lower prevalence among women can perhaps be attributed to lower prevalence of alcoholism, religiosity and flexible attitudes towards social skills and role-playing over their lifetimes.[27]

Another finding of great relevance for public health was the social indicators ascertained in this study. It was observed that young adults, aged between 25 and 44 years, individuals with higher education and individuals of white ethnicity presented higher prevalence of suicide. The place where suicide was committed most effectively was at home, and this proportion was twice as high as in other places, over the years. This can clearly be explained by the high rates of suicide that exist among young adults in low-income countries, due to inequality. Low quality of healthcare and poor access to it most likely play a role.

Some studies have shown that the adolescent and young adult population (between 20 and 50 years old) has experienced a significant increase in suicide rates.[28,29] Nevertheless, the elderly population (over 60 years old) still has the highest absolute rates, compared with the world average, and higher rates than in the population between 20 and 59 years old.[8,27-30] On the other hand, in the present study, the highest prevalence remained among adolescents and young adults. This may be explained by the higher work overloads and poorer quality of life in large urban population centers, as is the case of São Paulo, Brazil.

The higher suicide rates among young adults, individuals with higher education and individuals of white ethnicity forms an alarming scenario. It provides clear evidence that ethnicity, country of origin and country of settlement influence the risk of suicide, not least because cultural differences between countries may cause intergenerational and intrapsychic conflicts. So far, there is little evidence in the literature, from specific studies on factors that might be considered to be risk factors for suicide.[16] Higher schooling levels and white ethnicity were significant social factors in the city of São Paulo, for trigger suicidal actions, and preventive measures directed towards this segment of the population need to be implemented public.

The place of the suicidal act has been well discussed in the literature. The risk of suicide is around three to five times higher in hospital environments than in the population as a whole.[31] Most hospital-related cases are associated with chronic or terminal

Table 2. Proportional mortality due to suicide and standardized mortality rates for suicide in São Paulo (SP) (2000-2017), according to sociodemographic characteristics (age, education, ethnicity and place of occurrence)

Sociodemographic characteristics	Proportional mortality		Standardized coefficient
	n	%	
Age range (years)			
5-14	73	0.8	0.03
15-24	1,501	17.3	0.75
25-34	2,145	24.7	1.07
35-44	1,848	21.2	0.92
45-54	1,394	16.1	0.69
55-64	878	10.2	0.43
65-74	460	5.3	0.23
75 and more	381	4.4	0.19
Total	**8,680***	**100.0**	**4.34**
Schooling level (years)			
None	139	1.7	0.07
1 to 3	906	11.2	0.45
4 to 7	2,657	33.1	1.32
8 to 11	2,874	35.7	1.43
12 and more	1,466	18.3	0.73
Total	**8,042****	**100.0**	**4.02**
Ethnicity			
White	5,821	67.2	2.91
Black	487	5.6	0.24
East Asian	165	1.9	0.08
Brown	2,196	25.3	1.09
Indigenous	3	0.03	0.001
Total	**8,672*****	**100.0**	**4.33**
Place of occurrence			
Hospital	2,866	32.8	1.43
Home	4,157	47.8	2.07
Public highway	622	7.2	0.31
Healthcare centers	44	0.5	0.02
Others	1,015	11.7	0.50
Total	**8,704******	**100.0**	**4.35**

*46 without age information; **684 without education information; ***54 without ethnicity information; ****22 without location information.

illnesses that have become painful and debilitating.[31,32] However, in the present study, the opposite was observed, i.e. the prevalence of suicide was twice as high, over the 18-year period, in the home environment. Across the world, there is little data on the places where suicide attempts are made. If present, the quality of such data is low due to a lack of reliable statistics, which relates to underdiagnosis, misdiagnosis or non-diagnosis and reporting. The WHO does not receive information from any country in the world on this topic, although at least data from emergency rooms and somatic hospitals might be obtained, along with some self-reports. The results from the present study corroborate the data of Lovisi et al.,[14] which showed that the home was the most frequent scenario for suicides, accounting for 51%, followed by hospitals, with 26%. The predominant means used were hanging (47%), firearms (19%) and poisoning (14%).[14]

The limitation of the present study was that the real degrees of underestimation and underreporting of data were not ascertained. Thus, the true prevalence of suicide may have been greater, considering the extreme difficulty in accurately assessing the scale of suicidal acts and recording them.

CONCLUSION

Information from the city of São Paulo covering the years 2000-2017 led to the perception that suicide rates were high, with proportions of 4.7/100,000 inhabitants, and with high prevalence among young adults and males. The risk factors influencing high suicide rates were high schooling levels and white ethnicity. The crucial factor in successfully committing suicide was the home environment. One special aspect of primary prevention relates to the internet and especially social media, which provide a multitude of information for suicide prevention.

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COVID-19: laboratory diagnosis for clinicians. An updating article

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ABSTRACT

COVID-19 (coronavirus disease 2019) is an infectious disease caused by the new coronavirus associated with severe acute respiratory syndrome 2 (SARS-CoV-2). Coronaviridae comprises a large family, of which at least seven members are known to cause respiratory diseases in humans. Coronaviruses have the ability to infect virtually all major groups of animals and, eventually, can infect humans. SARS-CoV-2 is the third coronavirus to cross the species barrier and infect humans. This virus was identified in an outbreak of pneumonia cases in Wuhan city, Hubei province, China, in December 2019. Its entire genome is inscribed on a single strand of ribonucleic acid. Some proteins present on the surface of the virus act as facilitators for its entry into host cells, while others, apparently, are related to its pathogenesis. Coronaviruses are responsible for respiratory infections in humans and some animals. The infection is often mild to moderate in intensity, but some coronaviruses may cause serious illnesses, such as severe acute respiratory syndrome (SARS), which occurred in 2002, and the Middle East respiratory syndrome (MERS). Coronaviruses can activate an excessive and unregulated immune response, which may promote SARS development. Although the lungs are one of the target organs, the hypoxia mechanism is systemic and other organs begin to suffer both through lack of oxygen and through deregulation of inflammation control mechanisms.

INTRODUCTION

COVID-19 (coronavirus disease 2019) is an infectious disease caused by the new coronavirus associated with severe acute respiratory syndrome 2 (SARS-CoV-2). Coronaviridae comprises a large family, and at least seven coronaviruses are well known for causing respiratory diseases in humans. Coronaviruses have the ability to infect virtually all major groups of animals, among which some host other species that may infect humans. The current understanding is that SARS-CoV-2 is the third zoonotic coronavirus to have crossed the barrier between species and become capable of infecting humans over the past two decades.

THE CORONAVIRUS THAT CAUSES COVID-19

SARS-CoV-2 is a new betacoronavirus belonging to the large viral family of Coronaviridae, first identified in an outbreak of pneumonia cases in Wuhan city, Hubei province, China, in December 2019. The name COVID-19 was chosen as the name for this new infection as an acronym of coronavirus disease 2019, i.e. from corona "co", virus "vi", disease "d" and the number 19 indicating the year of its appearance. Efforts are being made by the World Health Organization (WHO) to ensure that the nomenclature of viruses and their infections no longer refers to geographical locations, as it did traditionally, in order to combat the stigma resulting from this practice.

The entire SARS-CoV-2 genome is inscribed on a single strand of RNA (ribonucleic acid). This type of virus undergoes genetic mutations more frequently than DNA (deoxyribonucleic acid) viruses, given that RNA viruses have less ability to correct any transcription errors.[1] SARS-CoV-2, in particular, is a single-stranded RNA virus that is capable of synthesizing about 29 different proteins. Some of these proteins are present on the surface of the virus and act as facilitators of its entry into host cells, while others, apparently, are related to its pathogenesis.

Characteristically, coronaviruses are responsible for respiratory infections in humans and some animals. Most of the time, the infections caused by viruses in this family are mild to

moderate in intensity and manifest as common colds. Some coronaviruses can cause more serious illnesses, such as severe acute respiratory syndrome (SARS), which occurred in 2002, and the Middle East respiratory syndrome (MERS), which still occurs in a well-defined region.

Coronaviruses can activate an excessive and unregulated immune response that is harmful to the host. These responses can contribute to the development of SARS. Autopsies on patients with COVID-19 worsened by SARS have revealed hyperactivation of effector T cells (CD8+) with high concentrations of cytotoxic granules. Reports describing the immune profile of patients critically ill with COVID-19 have suggested that hyperactivation of the cellular immune pathway may be a mediator of respiratory failure, shock and multiple organ failure.

SARS-CoV-2 binds to the human host cell via the ACE2 receptor (angiotensin-converting enzyme 2), and its input mechanism depends on sequential action by the serine protease TMPRSS2 enzyme. These data suggest that several therapeutic targets are possible, including the interleukin (IL)-6-STAT3 axis, which is associated with cytokine release syndrome (CRS).

Another structural protein of the virus is thought to have the ability to displace the iron that is present in hemoglobin. This would reduce the oxygen transportation capacity and provide the low level of saturation that is observed in some of the patients who evolve poorly. Additionally, release of iron ions in high quantities would cause oxidative damage, thus triggering an intense inflammatory process that might result in the condition known as a cytokine storm. Although the lungs are one of the target organs, the hypoxia mechanism is systemic and other organs start to suffer, both through lack of oxygen and through deregulation of the inflammation control mechanisms. Two other organs strongly affected are the liver and kidneys.

The clinical manifestations of COVID-19 can range from none, i.e. a totally asymptomatic state (which may be the case in up to 89% of individuals who become infected), to a situation characterized by mild to critical and fatal symptoms. The symptoms can develop between 2 to 14 days after exposure to the virus,[2] with an average incubation period of 5.1 days. Hence, the recommended quarantine period is usually 14 days.

Although the proportions may vary in the different populations affected, data provided by the Chinese Center for Disease Control and Prevention (CCDC) have shown that 81% of the patients had mild clinical manifestations; 14% of them had severe manifestations, including hypoxia; 5% of the cases were critical, with respiratory failure, multiple organ dysfunction and shock; and 2.3% of the cases were fatal.[3]

The course of the disease can last for around 16 days after a short incubation period, in mild to moderate cases; or can last for up to 10 weeks if there is a longer incubation period and a severe or fatal outcome. The following clinical scenarios have been estimated from various publications.

- Incubation period of 2 to 14 days (average 5 to 6 days) after infection
- Mild cases: duration of two weeks
- Severe and recovered cases: duration of three to six weeks

A person can be a transmitter even before symptoms appear, and can continue to be a transmitter until they disappear. The peak period for transmission is around five days after the onset of symptoms. It should be noted that because the pandemic is still new, the information provided here may change.[4]

LABORATORY DIAGNOSIS

When an infected person exhales droplets containing SARS-CoV-2 virions and they are inhaled by someone else, these droplets lodge on the nasal mucosa, which is formed by cells covered with ACE2 receptors. The virus binds with these receptors and thus is able to penetrate and hijack cell machinery in order to produce other virions and infect new cells. While viral multiplication is occurring, this person eliminates virions in large quantities, especially in the first week. This period can be asymptomatic or paucisymptomatic, with fever, dry cough, sore throat, anosmia, ageusia and severe headaches or body pain.[5] If the immune system is unable to stop the infection at this point, the virus progresses through the respiratory tract to the pulmonary alveoli, which are rich in ACE2 receptors. In the alveoli, leukocytes migrate due to the action of cytokines, which results in disruption of gas exchange, with pneumonia, characterized by productive cough, fever and dyspnea.[6]

In outpatients with flu-like symptoms, the chemosensory disorder causes loss of the sense of the smell and taste that is strongly associated with SARS-CoV-2 infection. This sign should be considered suggestive for clinical screening. Most people thus affected recover this function within weeks, in parallel with resolution of other symptoms.[7]

At this point, some patients' condition abruptly deteriorates, with development of SARS. Breathing becomes more difficult and oxygenation levels decline. Examinations on plain radiography and computed tomography of the chest reveal the typical ground-glass opacity. Patients need artificial ventilation and many die at this stage of the disease. Patients with severe COVID-19 conditions often develop acute hypoxemic respiratory failure and pneumonia, and 17% to 29% of them develop SARS. However, SARS in these cases differs in several aspects from the usual form of SARS, in which lung compliance is decreased. In patients with COVID-19, lung compliance is high.

The virus, probably with help from the immune response to it, can cause damage to the following other organs:

- Liver: about half of hospitalized patients show signs of liver changes.
- Kidneys: kidney damage, including kidney failure and the need for dialysis, is common in severe cases.
- Intestines: there may be a clinical presentation characterized by gastrointestinal symptoms, especially vomiting, diarrhea and abdominal pain. A "stomach" pain that may be associated with inflammation of the base of the lungs and diaphragm has been described. The lower gastrointestinal tract is rich in ACE2 receptors and about 20% of patients report diarrhea.
- Central nervous system: there have been reports of stroke, possibly due to formation of microthrombi, occurrences of seizures and cognitive changes.
- Eyes: in severe cases, occurrence of conjunctivitis has been described.
- Heart: an increase in cardiovascular events, notably acute myocardial infarction and thromboembolic events, and even disseminated intravascular coagulation, has been described.

MOLECULAR TESTS FOR SARS-COV-2: REAL-TIME REVERSE TRANSCRIPTION-POLYMERASE CHAIN REACTION (RRT-PCR)

The real-time reverse transcription-polymerase chain reaction with amplification (real-time RT-PCR with quantification, i.e. qRT-PCR) is the methodology that best applies for detection of the SARS-CoV-2 virus. With this technique, it is possible to identify viral RNA.

The genes considered for identification include N, E, S and RdRP. The international protocol developed by the Charité/Berlin Institute[8] and recommended by the Pan-American Health Organization (PAHO/WHO) has been used by most countries. Initially, laboratory confirmation depended on detection of two genetic markers but, considering the current high rate of virus circulation, confirmation can be given through detection of a single genetic marker.

The recommendation for laboratory confirmation of cases is that two different genetic markers should be detected (for example, the E gene followed by the RdRP gene, as previously described for the Charité protocol). Once circulation of the virus has become established and disseminated in a certain area or country, it would no longer be necessary to perform PCR for both genes, and confirmation would become possible through detection of a single genetic marker. The E gene has slightly higher sensitivity than the RdRP gene, so the Ministry of Health suggests prioritizing the E gene as the marker of choice.[8]

To improve the responsiveness of the public network, rapid molecular tests that can be processed on the automated GeneXpert platform (Cepheid) may be made available in Brazil. This is the same platform as used in the rapid test network for tuberculosis. This test performs qualitative in vitro detection of SARS-CoV-2 nucleic acid through automated real-time PCR, targeting the E and N2 genes, in nasopharyngeal swabs or nasal aspirate/wash specimens from suspected cases of COVID-19.[8]

The SARS-CoV-2 genome was quickly sequenced and was found to show 80% similarity to the SARS-CoV genome and 50% similarity to the MERS-CoV genome. The molecular laboratory diagnosis of COVID-19, in its initial phase, can be made from material collected from the upper respiratory tract (nasopharynx or oropharynx) or from the lower respiratory tract (sputum, tracheal aspirate or bronchoalveolar lavage) and is based on detection of specific viral nucleic acid. Because SARS-CoV-2 is an RNA virus, its identification requires generation of a complementary DNA strand (cDNA), which is obtained through the action of the reverse transcriptase enzyme. After reverse transcription, two primers that promote amplification of two genetic targets are inserted. With a complementary probe, it is possible to observe the molecular content corresponding to that of the target infectious agent.

Important barriers impeding widespread use of RT-PCR for detection of the new coronavirus in Brazil currently exist. Notably, the quantity of test kits and equipment available in this country is insufficient. Moreover, this methodology is laborious when the extraction and testing are manual, which has given rise to a large number of tests pending, mainly, but not exclusively, within the public network of the Central Public Health Laboratories (Laboratórios Centrais de Saúde Pública, LACENs). Nonetheless, it is likely that this scenario will return to normal, considering that production of this test is being greatly stimulated.

This laboratory test is very specific. However, its sensitivity can vary, mainly due to pre-analytical variables such as:

- Stage of infection and viral load in secretions and excretions, mainly with regard to upper respiratory tract samples collected less than three days and more than ten days since the beginning of the contamination;
- Place of collection: It is known that materials from the lower respiratory tract (sputum or bronchoalveolar lavage) tend to be more positive than those from the upper respiratory tract (combined nasal and oropharyngeal swabs);
- Collection, transportation and storage techniques used for samples until their analysis, to avoid degradation of the RNA present in the specimen.

RT-PCR directly detects the presence of specific components of the virus genome. Therefore, it should be used to diagnose the disease in the asymptomatic or pre-symptomatic phase, or in the symptomatic phase within the first 12 days after the onset of symptoms. There are not enough data in the Brazilian literature yet to have an accurate picture regarding the sensitivity and specificity of this methodology in this country. For reference only, the following sensitivity rates can be stated (true positive results

in the presence of the disease): 93% for investigations on bronchoalveolar lavage, 72% on sputum, 63% on nasal material and 32% on oropharyngeal material. Detection of the virus in blood, feces, urine and saliva is also possible, but use of these samples for routine diagnosis has not yet been developed. Many of the virus detection studies were carried out only through viewing the virus through electron microscopy and virus neutralization techniques.

RT-PCR for diagnosing SAR-CoV-2 is considered highly specific, and a positive result confirms the presence of the infection ("gold standard"). However, because of the aforementioned problems regarding sensitivity, negative results do not rule its presence out, and it may be necessary to repeat the test on another sample after a few days.

In order to ensure that the tests that are requested are performed, it is essential that the medical order is clear and objective. It is recommended that the requesting physician should indicate the material that is to be collected (for example, secretions from the oropharynx or nasopharynx, sputum, tracheal aspirate or bronchoalveolar lavage) and explain which test is to be performed, i.e. RT-PCR for SARS-CoV-2.

MOLECULAR PANELS FOR OTHER RESPIRATORY VIRUSES

According to guidance from the Ministry of Health,[8] patients with SARS who present a negative molecular test for COVID-19 need to undergo testing for other respiratory viruses, including influenza.

Respiratory viruses are the pathogens most frequently associated with acute respiratory infections (ARI), with high morbidity and mortality in children in the first year of life and in immunocompromised adults and the elderly.

Pneumonia is the most common cause of fatal outcomes. Clarifying the viral cause avoids undue administration of antimicrobials and allows identification of the causal virus, thus making it possible to study outbreaks.

For this purpose, samples of respiratory tract secretions can be collected to be subjected to molecular diagnostic tests for detection of specific nucleic acids of various respiratory viruses. These multiplexed molecular panels are popularly known as "viromes". Their scope may vary between laboratories, but they generally have the ability to detect influenza, parainfluenza, coronavirus, respiratory syncytial virus, adenovirus, metapneumovirus, enterovirus, bocavirus and rhinovirus.

A Chinese study reported that coinfection with other respiratory viruses would be rare.[9] Another study on the incidence of coinfection showed that molecular detection of a pathogen other than SARS-CoV-2 was not sufficient to ensure absence of infection with the new coronavirus. These results do not support routine use of virome panels, given their low effectiveness in this context. However, one possible exception could be the use of neuraminidase inhibitors in patients infected or coinfected by influenza.[10]

Considering that viral coinfections are relatively frequent, according to the guide of the Influenza Surveillance Laboratory Network of Brazil,[11] all patients presenting suspected influenza-like illness (ILI) or SARS should be tested for the COVID-19 virus and other respiratory pathogens, using usual laboratory procedures.

IMMUNOLOGICAL LABORATORY TESTS

In the light of the WHO guidance on the need for mass testing of populations, given the expansion of the pandemic and the current barriers to carrying out RT-PCR at rates compatible with demand, companies producing laboratory diagnostic reagents have started to develop tests for investigating antibodies and antigens related to the virus. The vast existing literature highlights that coronaviruses are immunogenic infectious agents, capable of generating humoral and cellular immune responses in the host.

Just like in all other viral infections, the body reacts to the presence of this virus by producing antibodies, initially those of the immunoglobulin A (IgA) and immunoglobulin M (IgM) classes, and subsequently those of the immunoglobulin G (IgG) class. Presence of specific antibodies against antigenic determinants of SARS-CoV-2 indicates that there was a previous infection, but considering that this is an infectious agent that was only introduced into the community very recently, occurrence of cross-reactions with other coronaviruses currently in community circulation cannot be ruled out. Such occurrences could compromise the specificity of the tests.

Some time is needed for production of these antibodies. On average, the time required is 7 to 10 days after the onset of symptoms for the IgM class antibodies, and 10 days or more for IgG. These numbers clearly indicate that early detection of antibodies is possible , but only in a limited number of patients. As the days go by, the concentrations of both antibody classes increase, and the chance of false-negative results decreases. While the search for viral particles is carried out mainly using secretions and washings, the search for and quantification of antibodies can be carried out using capillary blood, whole blood, serum or plasma. Thus, blood collection is required, either from a fingertip for the rapid test, or from a vein to obtain whole blood.

Several immunological tests are already available on the market, certified by the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária, ANVISA), for investigations on IgA, IgM and IgG antibodies and viral antigens. Several methodologies are available:

Automated methodologies: These include the enzyme-linked immunosorbent assay (ELISA), chemiluminescence and electrochemiluminescence. Investigation and quantification of antibodies using these methods are carried out on whole blood, serum or

plasma, in a laboratory environment, using analytical equipment that is capable of quantifying antibody levels and performing tests on paired samples, 28 days apart. In general, these methods are more sensitive and specific and less dependent on the operator.

Methodologies for "rapid tests", more appropriately called **"point-of-care testing"** (POCT): These consist mainly of immunochromatography. They involve investigation of antibodies in whole blood, serum or plasma using manual methods, which are performed quickly on individual devices and provide results within 10 to 30 minutes. At present, some tests of this type are reported to present performance deficiencies. These tests are still at the stage of evaluation and validation, at both public and private clinical laboratories.

Some rapid tests that are available for investigation of viral antigens in material collected from the nostrils and throat have not yet been studied regarding their effectiveness in relation to molecular tests.

The different performance qualities of the rapid tests that are currently available arise from a variety of technical issues, such as differences in the purification processes used for coronavirus viral antigens (S and N). The aims in these processes are to avoid loss of their three-dimensional format and thus to adequately recognize antibodies (i.e. to maintain antigen quality), achieve the ideal degree of surface sensitization and ensure the quality of reactants, storage and transportation, among other matters.

The literature relating to antibody production in response to antigen stimulus shows that this is an individual response. Therefore, the number of antibodies formed may vary and, consequently, the time of antibody detection may differ, although the vast majority of studies on coronavirus infections have indicated that these are already evident by the seventh or eighth day. Thus, it has been emphasized that patients may take shorter or longer times to manifest the infection. It has been concluded from these studies that awareness of the possible variability of the immunological window period is needed (i.e. the time that elapses between contamination and laboratory detection of antibodies).

It is not yet possible to say with certainty whether the antibodies thus formed are an effective defense against possible reinfection, i.e. whether they confer immunity and, if so, how long they last. It is also not yet possible to clearly state what the role of rapid serological tests for making individual diagnoses is, considering that non-reactive results do not rule out the possibility of SARS-CoV-2 infection. On the other hand, reactive results can lead to a false sense of security with regard to re-exposure to the virus. However, within the context of public health, the greatest utility of serological tests may lie in their use in population-based surveys.

In early April, the WHO recommended that rapid tests should be used for epidemiological purposes only and contraindicated their use for diagnosis. In cases in which RT-PCR tests are non-reactive but COVID-19 infection is suspected, serological tests performed on sequential samples can assist in clarifying the diagnosis.[12]

SEROPOSITIVITY CERTIFICATE

At the present time, the best definition for an "immunity passport", would perhaps be that this is a "seropositivity certificate". There is strong pressure for social life to return to the old "normal" pattern, i.e. for there to be a loosening of social distancing. With the recent development of laboratory tests that detect the presence of antibodies, an expectation has been created that people in whom antibodies against SARS-CoV-2 are potentially detected could be released to resume their usual activities. Studies in this direction are being carried out in some countries of the European Union, especially Germany, and in China and the United States. At the moment, the following elements need to be considered:

- Antibodies start to be detected only one to two weeks after infection;
- It is not yet known whether antibodies detectable through current tests are capable of conferring long-lasting immunity (i.e. whether they would be protective antibodies), or for how long;
- The new tests have been released in a speeded-up manner and still need to be carefully validated.

In the case of SARS in 2002, antibodies were present for two to three years and in the case of MERS, for one year. In the case of COVID-19, this information would be important for making it possible to determine, for example, the retest interval that would be required in order to enable certification of immunity on an ongoing basis and to organize vaccination programs.

It is not certain that the appearance of antibodies indicates that the person is no longer a transmitter or that he/she becomes immune, and for how long. Some people have been shown to carry the virus for a long time (a few weeks).

There are ethical issues. Even if the percentage of false-reactants is not large, non-immune people would be considered immune and exposed, and susceptible people could be discriminated against in the job market. And lastly, it is necessary to avoid enabling trade in this type of certificate, including through fraud.

LABORATORY EVALUATION OF THE INFLAMMATORY STORM

Cytokines are low molecular weight proteins that are released by various types of cells, especially those that make up the immune system, and have a role in intercellular signaling. Among various actions, the cytokines released by the cells of the immune system act to modulate the inflammatory response, from the time when the organism is attacked by infectious agents. The term "cytokine" is derived from two Greek words "cyto" for cell, and "kinos" for movement. The rationale for this nomenclature,

which emphasizes the mobile nature of these cells, is based on the fact that, because they are small molecules, they have great mobility in body fluids and have the ability to recruit different cells of the immune system to act together.

The inflammatory response is an extremely complex event, involving numerous cellular and humoral agents. Among other purposes, it seeks to identify, isolate, neutralize and eliminate agents that are harmful to the body. It involves participation of cellular and humoral elements that act in a coordinated manner, with self-modulation of their intensity of response to an invading agent. However, dysregulation of the inflammatory response may sometimes occur. In these situations, excessive quantities of cytokines are released, and these activate and recruit cells of the immune system such that an oversized response is generated, thus resulting in hyperinflammation. This condition is called a "cytokine storm" and results in generation of a microenvironment that is harmful to the organism itself.

The cytokine storm concept apparently began to be studied in the early 1990s. It was correlated with several viral infections and was recognized during the SARS outbreak in 2002, as a factor presenting a high risk of mortality. The term was only coined in 2005, when avian influenza caused by the H5N1 virus occurred, and its occurrence was linked to a high mortality rate due to an exacerbated pro-inflammatory response. In some non-infectious diseases, such as multiple sclerosis, cytokine storms can also be observed. Since then, cytokine storms have been described in relation to several respiratory diseases caused by viruses of the coronavirus family, such as MERS in 2012 and, more recently, SARS-CoV-2.[13] The main cause of death in cases of COVID-19 is respiratory failure caused by SARS.[14]

Another syndrome related to the immune response is secondary hemophagocytic lymphohistiocytosis (sHLH), a little-known condition that is characterized by fulminant hypercytokinemia and rapidly evolves to multiple organ failure. It has been described in about 3.7% to 4.3% of sepsis cases,[15] but it is more often described in viral infections.[16] Clinically, it is characterized by the presence of constant fever, cytopenia and high levels of ferritin, interleukins (IL), granulocyte-colony stimulating factor (GCSF), interferon-γ inducible protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein 1-α and tumor necrosis factor-α.[17]

SARS occurs in about 50% of patients with sHLH.[18,19] Comparison of groups of patients with SARS in association with the new coronavirus via laboratory results has shown significant differences between survivors and non-survivors. The most striking differential parameters include leukocyte counts, absolute lymphocyte and platelet counts and the concentrations of albumin, total bilirubin, serum urea, creatinine, myoglobin, cardiac troponin, C-reactive protein (CRP) and interleukin-6 (IL-6).

In patients with COVID-19, ferritin and IL-6 levels have been shown to be good predictors of fatality, as shown in **Table 1**, adapted from the work by Ruan et al.[14] This emphasizes the hypothesis of the presence of a hyperinflammatory response.

OTHER LABORATORY PARAMETERS

COVID-19 is a systemic infection with significant impacts on the hematopoietic system and hemostasis. Lymphopenia can be considered to be a cardinal laboratory sign, and is potentially prognostic. The neutrophil/lymphocyte and peak platelet/lymphocyte ratios can help to assess the severity of cases. Over the

Table 1. Laboratory parameters among patients with COVID-19, as modified by Rual et al.[14]

Laboratory parameters	Reference range	Non-survivors mean (SD)	Survivors mean (SD)	P-value
Time between symptom onset and collection, in days		11.6 (6.8)	9.8 (4.3)	0.07
Leukocytes, × 10^9/l	3.50-9.50	10.62 (4.76)	6.76 (3.49)	< 0.001
Lymphocytes, × 10^9/l	1.10-3.20	0.60 (0.32)	1.42 (2.14)	< 0.001
Hemoglobin, g/l	130.0-175.0	127.0 (16.7)	127.6 (16.3)	0.82
Platelets, × 10^9/l	125.0-350.0	173.6 (67.7)	222.1 (78.0)	< 0.001
Serum albumin, mg/dl	3.50-5.20	2.88 (0.38)	3.27 (0.38)	< 0.001
Serum alanine aminotransferase, U/l	9.0-50.0	170.8 (991.6)	48.68 (83.1)	0.35
Serum aspartate aminotransferase, U/l	15.0-40.0	288.9 (1875.5)	40.7 (57.8)	0.31
Total serum bilirubin, mg/dl	0.3-1.5	1.1 (0.63)	0.75 (0.40)	0.001
Serum creatine, mg/dl	0.50-1.50	1.03 (0.64)	0.81 (0.27)	0.02
Serum creatine kinase, U/l	50.0-310.0	319.4 (838.5)	231.7 (862.3)	0.56
Serum lactic dehydrogenase, U/l	120.0-250.0	905.8 (2619.1)	297.9 (110.4)	0.08
Serum cardiac troponin, pg/ml	2.0-28.0	30.3 (151.0)	3.5 (6.2)	< 0.001
Serum myoglobin, ng/ml	0.0-146.9	258.9 (307.6)	77.7 (136.1)	< 0.001
Serum C-reactive protein, mg/l	0.0-5.0	126.6 (106.3)	34.1 (54.5)	< 0.001
Serum interleukin-6, pg/ml	0.0-7.0	11.4 (8.5)	6.8 (3.61)	< 0.001
Serum ferritin, ng/ml	21.8-274.7	1297.6 (1030.9)	614.0 (752.2)	< 0.001

SD = standard deviation.

course of the disease, a longitudinal assessment of the dynamics of lymphocyte counts and inflammatory indices (including lactic dehydrogenase, CRP and IL-6) can help to identify cases with a worse prognosis and indicate the need for more aggressive interventions. Other biomarkers, such as procalcitonin and ferritin, are also being considered as factors that indicate worse prognosis.

Hypercoagulability is common in patients who are hospitalized due to COVID-19. Elevated D-dimer levels have been reported consistently, with emphasis on progressive increase in their levels, thus indicating a worsening of the condition. Other abnormalities of coagulation tests, such as prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT) and elevation of fibrin degradation products and severe thrombocytopenia, indicate the possibility of occurrences of disseminated intravascular coagulation (DIC), which needs to be monitored and should undergo early intervention.

Both hospitalized patients and outpatients with COVID-19 are at increased risk of venous thromboembolism. Therefore, early and prolonged pharmacological thromboprophylaxis with low molecular weight heparin is recommended.[18]

Other relevant laboratory parameters include lymphopenia and elevations of PT, D-dimer and lactic dehydrogenase activity, which have already been observed in the initial phase of response to the presence of the virus. With the onset of pneumonia and the consequent hypoxia, there is an increase in transaminase levels increase, which indicates occurrence of significant hepatocellular distress. Increased liver enzyme activity is an important indicator of the severity of the condition. When the most severe stage of hyperinflammation is reached, accompanied by coagulopathy, inflammation markers such as CRP, ferritin, troponin and brain natriuretic peptide (BNP) will be at very high levels, thus characterizing an inflammatory storm.

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Social media during a pandemic: bridge or burden?

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Dear Editor,

Since the late 2000s, humanity has gradually moved towards accessing the internet with the aim of seeking social media rather than for any other purpose. The web has undoubtedly become empowered over the last decade as a global communication tool.[1]

Many authors have underscored a central issue regarding social media: while networks enable interactions with larger numbers of people, they also inevitably lead towards a reduction in interpersonal communication within the family and within the physical environment.[2] The decrease in time spent on direct face-to-face interaction can contribute to psychiatric and psychological problems. In fact, recent studies have highlighted that longer times spent on social media can give rise to distorted impressions of oneself and correlate with the intensity of depressive symptoms.[3]

Interestingly, Facebook users tend to perceive others as happier than themselves and, thus, are more likely to express the feeling that "life is not fair".[4] This misconception is problematic, since perceiving others as happier and more successful can act as a stressor for mental dysfunction.[1] A huge paradox has consequently arisen: people are increasingly in contact with one another throughout a myriad of screens and devices, but have never before felt so lonely.

Nonetheless, the boom in social media has also been a bright spot for mental health. Different researchers have shed some light over positive uses of online communication with friends and family, and the main results indicate that online communication is associated with decreased depression.[5] In other words, use of social media to strengthen preexisting affective bonds seems to function as a factor of social insertion, thereby protecting individuals against mental illnesses. Moreover, different web-based tools focusing on screening for psychiatric symptoms and clinical assessments have been advancing by leaps and bounds.

The harmful potential of social media seems, thus, to depend on people's own *modus operandi*. In other words, use of computers has been cautiously seen as a useful tool if well used, but has also been seen as a potentially insidious enemy, if used without a suitable purpose and not in keeping with the overall scenario.

Hence, all in all, in relation to the current scenario of the COVID-19 pandemic, the question that arises is the following: Can use of social media aid in overcoming the burden of inevitable isolation?

Regarding the current medical literature, no specific studies with emphasis on social media and pandemics have yet been conducted. However, two main strategies can be derived from data on daily use of social media that are already available. Firstly, use of social media can become a real-time communication strategy for helping data and information to circulate during a pandemic. This follows from the recommendations made in the current COVID-19 pandemic, in which widespread use of cutting-edge information technology to raise awareness about some particular event has been highlighted as a fundamental approach towards dealing with the crisis. Secondly, use of social media can put people side by side if they have been forced apart and have already become stressed, as commonly seen during quarantines. Hence, social media have the ability to bring people closer together when they are unable to physically see each other.

In conclusion, it is not a matter of how much use is made of social media, but rather an issue of the way in which these media and new technologies are used: this is the key point underscoring the usefulness of online and virtual social interactions.

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Use of smartphone-based instant messaging services in medical practice: a cross-sectional study

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Dear Editor,

In response to the article titled "Use of smartphone-based instant messaging services in medical practice: a cross-sectional study" published in your esteemed journal, which is a well thought-out and well-written paper, I would like to raise few points regarding this study.

The article reported that doctors and medical students have used instant messaging services to discuss clinical cases, allow interactions between healthcare professionals and patients or disseminate knowledge. However, ethical and legal limitations to the use of telemedicine need to be discussed.[1]

Telemedicine can be used to serve the population and can be used by healthcare professionals in the field of education. Advances in medical legislation will be necessary for enabling national certification of doctors so that they can work both nationwide and internationally.

Moreover, security in electronic systems needs to be guaranteed so as to preserve patient data. Unfortunately, encrypted information systems remain much less secure than those based on old paper records.

Care is needed to ensure that telemedicine is not used just to reduce investment in healthcare but is used to increase the efficiency of the provision of medical services. The list of activities that can be conducted via telemedicine and the mandatory technical requirements for these activities need to be widely discussed. These requirements need to be adhered to, so as to ensure that work done through telemedicine is of good quality. Verbal consent needs to be obtained, so that the scope of what telehealth entails is delineated, along with the benefits and risks of using telehealth to perform limited examinations, and any other state-designated requirements. Situations in which these examinations are not live and are therefore incomplete should be highlighted.

In this manner, an excellent return can be obtained for society, thereby ensuring continuous education for healthcare professionals and facilitating healthcare management. Telemedicine can be useful for saving lives through social distancing in a hyperendemic area, while also remaining available to provide care for needy patients.[2]

However, doctors who use telemedicine are responsible for the quality of patient care and should not opt for telemedicine consultations unless they consider that this is the best option available. To make this decision, they should take into account quality, access and cost. This new technology brings a variety of benefits, including: acquisition of new knowledge by the healthcare team, diagnoses for patients in regions with a shortage of specialists and avoidance of long-distance travel for doctors and patients.

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Author's contribution: Martins TGS: conception and design of the work, revision of the work and final approval

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INSTRUCTIONS FOR AUTHORS

Scope and indexing

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is published bimonthly by Associação Paulista de Medicina, a regional medical association in Brazil.

The Journal accepts articles in English in the fields of evidence-based health, including internal medicine, epidemiology and public health, specialized medicine (gynecology & obstetrics, mental health, surgery, pediatrics, urology, neurology and many others), and also physical therapy, speech therapy, psychology, nursing and healthcare management/administration.

São Paulo Medical Journal's articles are indexed in MEDLINE, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

Editorial policy

Papers with a commercial objective will not be accepted: please review the Journal's conflicts of interest policy below.

São Paulo Medical Journal is an open-access publication. This means that it publishes full texts online with free access for readers.

São Paulo Medical Journal does not charge authors any "open access fees" and submission is free for all. Associação Paulista de Medicina provides financial support for the Journal.

Articles accepted for publication become the Journal's property for copyright purposes, in accordance with Creative Commons attribution type BY.

Transparency and integrity: guidelines for writing

The Journal recommends that all articles submitted should comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals,[1] as updated in the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. These standards were created and published by the International Committee of Medical Journal Editors (ICMJE) as a step towards integrity and transparency in science reporting and they were updated in December 2018.[1]

All studies published in *São Paulo Medical Journal* must be described in accordance with the specific guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE),[5,6] case reports (CARE)[7] and accuracy studies on diagnostic tests (STARD).[8,9] These guidelines ensure that all methodological procedures have been described, and that no result has been omitted. If none of the above reporting guidelines are adequate for the study design, authors are encouraged to visit the EQUATOR Network website (http://www.equator-network.org/) to search for appropriate tools.

Conflicts of interest

Authors are required to describe any conflicts of interest that may exist regarding the research or the publication of the article. Failure to disclose any conflicts of interest is a form of misconduct.

Conflicts of interest may be financial or non-financial. The Journal recommends that the item "Conflicts of interest" at http://www.icmje.org should be read to obtain clarifications regarding what may or may not be considered to be a conflict of interest. The existence and declaration of conflicts of interest is not an impediment to publication at all.

Acknowledgements and funding

Grants, bursaries and any other financial support for studies must be mentioned separately, after the references, in a section named "Acknowledgements." Any financial support should be acknowledged, always with the funding agency name, and with the protocol number whenever possible. Donation of materials used in the research can and should be acknowledged too.

This section should also be used to acknowledge any other contributions from individuals or professionals who have helped in producing or reviewing the study, and whose contributions to the publication do not constitute authorship.

Authorship

The Journal supports the position taken by the ICMJE (http://www.icmje.org) regarding authorship. All authors should read ICMJE's recommendations to obtain clarifications regarding the criteria for authorship and to verify whether all of them have made enough contributions to be considered authors.[10]

All authors of articles published in *São Paulo Medical Journal* need to have contributed actively to the discussion of the study results and should review and approve the final version that is to be released. If one author has not contributed enough or has not approved the final version of the manuscript, he/she must be transferred to the Acknowledgement section.

The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its publication. However, *São Paulo Medical Journal* and ICMJE consider that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text. Contributions such as data collection only do not constitute authorship.

The addition or deletion of authors' names in the manuscript byline is possible only if the corresponding author provides the reason for the rearrangement and a written signed agreement from all authors. Modifications to the order of the authors are possible, but also need to be justified. Authors whose names are removed or inserted must agree with this in writing. Publication of the article cannot proceed without a declaration of authorship contributions signed by all authors.

São Paulo Medical Journal supports the ORCID initiative. All authors should create an ORCID identification (ID) record (in www.orcid.org) before submitting their article and should link the submission to their existing ORCID ID in the electronic submission system. ORCID identifications help to distinguish researchers with similar names, give credit to contributors and link authors to their professional affiliations. In addition, this may increase the ability of search engines to retrieve articles.

Redundant or duplicate publication

São Paulo Medical Journal will avoid publishing redundant or duplicate articles. The Journal agrees with the ICMJE definition of redundant publication,[11] i.e. an attempt to report or publish the same results from a study twice. This includes but is not limited to publication of patient cohort data that has already been published, without clear reference to the previous publication. In situations in which authors are making a secondary analysis on data that has already published elsewhere, they must state this clearly. Moreover, the outcomes assessed in each analysis should be clearly differentiated.

The Journal's peer review policy and procedures

After receipt of the article through the electronic submission system, it will be read by the editorial team, who will check whether the text complies with the Journal's Instructions for Authors regarding format. The Journal has adopted the *CrossRef Similarity Check* system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be promptly rejected. Self-plagiarism will also be monitored.

When the general format of the manuscript is deemed acceptable and fully compliant with these Instructions for Authors, and only then, the editorial team will submit the article to the Editor-in-Chief, who will firstly evaluate its scope. If the editor finds that the topic is of interest for publication, he will assign at least two reviewers/referees with expertise in the theme, to evaluate the quality of the study. After a period varying from one to several weeks, the authors will then receive the reviewers' evaluations and will be required to provide all further information requested and the corrections that may be necessary for publication. These reviewers, as well as the Editorial Team and the Editor-in-Chief, may also deem the article to be unsuitable for publication by *São Paulo Medical Journal* at this point.

At the time of manuscript submission, the authors will be asked to indicate the names of three to five referees. All of them should be from outside the institution where the authors work and at least two should preferably be from outside Brazil. The Editor-in-Chief is free to choose them to review the paper or to rely on the *São Paulo Medical Journal's* Editorial Board alone.

Articles will be rejected without peer review if:

- they do not present Ethics Committee approval (or a justification for the absence of this);
- they fail to adhere to the format for text and figures described here.

After peer review

Peer reviewers, associated editors and the Editor-in-Chief may ask for clarifications or changes to be made to the manuscript. The authors should then send their article back to the Journal, with the modifications made as requested. Changes to the text should be highlighted (in a different color or using a text editor tool to track changes). Failure to show the changes clearly might result in the paper being returned to the authors.

The modified article must be accompanied by a letter answering the referees' comments, point by point. The modified article and the response letter are presented to the editorial team and reviewers, who will verify whether the problems have been resolved adequately. The text and the reviewers' final evaluations, along with the response letter, will then be sent to the Editor-in-Chief for a decision.

Manuscripts that are found to be suitable for publication through their scientific merit will be considered "provisionally accepted". However, all articles will subsequently be scrutinized to check for any problems regarding the reporting, i.e. sentence construction, spelling, grammar, numerical/statistical problems, bibliographical references and other matters that may arise, especially in the Methods section. The adherence to reporting guidelines will be checked at this point, and the staff will point out any information regarding methodology or results that the authors should provide. This is done in order to ensure transparency and integrity of publication, and to allow reproducibility.

The editorial team will then provide page proofs for the authors to review and approve. No article is published without this final author approval. All authors should review the proof, although the Journal asks the corresponding author to give final approval.

Submission

Articles should be submitted only after they have been formatted as described below. Texts must be submitted exclusively through the Internet, using the Journal's electronic submission system, which is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

The manuscript should be divided into two files. The first of these, the main document ("blinded"), should contain the article title, article type, keywords and abstract, article text, references and tables, but must omit all information about the authors. The second of these, the "title page", should contain all the information about the authors.

The corresponding author is responsible for the submission. However, all authors should approve the final version of the manuscript that is to be submitted and should be aware of and approve any changes that might be made after peer review.

Covering letter

All manuscripts must be submitted with a covering letter signed at least by the corresponding author. The letter must contain the following five essential items relating to the manuscript:

1. a declaration that the manuscript is original and that the text is not under consideration by any other journal;

2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports;
4. a brief description of the contributorship of each author;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number in the PROSPERO database. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Sample size

All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Short communications

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Each author should present his/her ORCID identification number (as obtained from www.orcid.org);
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. Each author should indicate a valid, up-to-date email address for contact;
7. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);
8. Place or institution where the work was developed, city and country.
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh. These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the "doi" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of

sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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A APM, em parceria com a **Prontmed**, oferece o único prontuário eletrônico feito de médico para médico.

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